

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
18 April 2002 (18.04.2002)

PCT

(10) International Publication Number
WO 02/30924 A1

(51) International Patent Classification⁷: C07D 405/12, A61K 31/517, A61P 35/00

(74) Agent: TAIT, Brian; AstraZeneca, Global Intellectual Property, P.O. Box 272, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4GR (GB).

(21) International Application Number: PCT/GB01/04498

(22) International Filing Date: 9 October 2001 (09.10.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
00402844.5 13 October 2000 (13.10.2000) EP

(71) Applicant (for all designated States except MG, US): ASTRAZENECA AB [SE/SE]; S-151 85 Sodertalje (SE).

(71) Applicant (for MG only): ASTRAZENECA UK LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): LAMBERT, Christine, Marie, Paul [BE/FR]; Z.I. La Pompelle, Boîte postale 1050, F-51689 Reims Cedex 2 (FR). PLE, Patrick [FR/FR]; Z.I. La Pompelle, Boîte postale 1050, F-51689 Reims Cedex 2 (FR).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

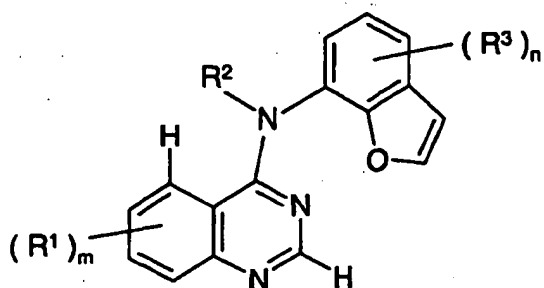
(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: QUINAZOLINE DERIVATIVES WITH ANTI-TUMOUR ACTIVITY



(I)

(57) Abstract: The invention concerns quinazoline derivatives of Formula (I) wherein each of m, R¹, n, R² and R³ have any of the meanings defined in the description; processes for their preparation, pharmaceutical compositions containing them and their use in the manufacture of a medicament for use as an anti-invasive agent in the containment and/or treatment of solid tumour disease.

WO 02/30924 A1

- 1 -

QUINAZOLINE DERIVATIVES WITH ANTI-TUMOUR ACTIVITY

The invention concerns certain novel quinazoline derivatives, or pharmaceutically-acceptable salts thereof, which possess anti-tumour activity and are accordingly useful in methods of treatment of the human or animal body. The invention also concerns processes for the manufacture of said quinazoline derivatives, to pharmaceutical compositions containing them and to their use in therapeutic methods, for example in the manufacture of medicaments for use in the prevention or treatment of solid tumour disease in a warm-blooded animal such as man.

Many of the current treatment regimes for cell proliferation diseases such as psoriasis and cancer utilise compounds which inhibit DNA synthesis. Such compounds are toxic to cells generally but their toxic effect on rapidly dividing cells such as tumour cells can be beneficial. Alternative approaches to anti-tumour agents which act by mechanisms other than the inhibition of DNA synthesis have the potential to display enhanced selectivity of action.

In recent years it has been discovered that a cell may become cancerous by virtue of the transformation of a portion of its DNA into an oncogene i.e. a gene which, on activation, leads to the formation of malignant tumour cells (Bradshaw, Mutagenesis, 1986, 1, 91). Several such oncogenes give rise to the production of peptides which are receptors for growth factors. Activation of the growth factor receptor complex subsequently leads to an increase in cell proliferation. It is known, for example, that several oncogenes encode tyrosine kinase enzymes and that certain growth factor receptors are also tyrosine kinase enzymes (Yarden *et al.*, Ann. Rev. Biochem., 1988, 57, 443; Larsen *et al.*, Ann. Reports in Med. Chem., 1989, Chpt. 13). The first group of tyrosine kinases to be identified arose from such viral oncogenes, for example pp60^{v-Src} tyrosine kinase (otherwise known as v-Src), and the corresponding tyrosine kinases in normal cells, for example pp60^{c-Src} tyrosine kinase (otherwise known as c-Src).

Receptor tyrosine kinases are important in the transmission of biochemical signals which initiate cell replication. They are large enzymes which span the cell membrane and possess an extracellular binding domain for growth factors such as epidermal growth factor (EGF) and an intracellular portion which functions as a kinase to phosphorylate tyrosine amino acids in proteins and hence to influence cell proliferation. Various classes of receptor tyrosine kinases are known (Wilks, Advances in Cancer Research, 1993, 60, 43-73) based on

- 2 -

families of growth factors which bind to different receptor tyrosine kinases. The classification includes Class I receptor tyrosine kinases comprising the EGF family of receptor tyrosine kinases such as the EGF, TGF α , Neu and erbB receptors, Class II receptor tyrosine kinases comprising the insulin family of receptor tyrosine kinases such as the insulin and IGF1 receptors and insulin-related receptor (IRR) and Class III receptor tyrosine kinases comprising the platelet-derived growth factor (PDGF) family of receptor tyrosine kinases such as the PDGF α , PDGF β and colony-stimulating factor 1 (CSF1) receptors.

It is also known that certain tyrosine kinases belong to the class of non-receptor tyrosine kinases which are located intracellularly and are involved in the transmission of biochemical signals such as those that influence tumour cell motility, dissemination and invasiveness and subsequently metastatic tumour growth (Ullrich *et al.*, Cell, 1990, 61, 203-212, Bolen *et al.*, FASEB J., 1992, 6, 3403-3409, Brickell *et al.*, Critical Reviews in Oncogenesis, 1992, 3, 401-406, Bohlen *et al.*, Oncogene, 1993, 8, 2025-2031, Courtneidge *et al.*, Semin. Cancer Biol., 1994, 5, 239-246, Lauffenburger *et al.*, Cell, 1996, 84, 359-369, Hanks *et al.*, BioEssays, 1996, 19, 137-145, Parsons *et al.*, Current Opinion in Cell Biology, 1997, 9, 187-192, Brown *et al.*, Biochimica et Biophysica Acta, 1996, 1287, 121-149 and Schlaepfer *et al.*, Progress in Biophysics and Molecular Biology, 1999, 71, 435-478). Various classes of non-receptor tyrosine kinases are known including the Src family such as the Src, Lyn and Yes tyrosine kinases, the Abl family such as Abl and Arg and the Jak family such as Jak 1 and Tyk 2.

It is known that the Src family of non-receptor tyrosine kinases are highly regulated in normal cells and in the absence of extracellular stimuli are maintained in an inactive conformation. However, some Src family members, for example c-Src tyrosine kinase, is frequently significantly activated (when compared to normal cell levels) in common human cancers such as gastrointestinal cancer, for example colon, rectal and stomach cancer (Cartwright *et al.*, Proc. Natl. Acad. Sci. USA, 1990, 87, 558-562 and Mao *et al.*, Oncogene, 1997, 15, 3083-3090), and breast cancer (Muthuswamy *et al.*, Oncogene, 1995, 11, 1801-1810). The Src family of non-receptor tyrosine kinases has also been located in other common human cancers such as non-small cell lung cancers (NSCLCs) including adenocarcinomas and squamous cell cancer of the lung (Mazurenko *et al.*, European Journal of Cancer, 1992, 28, 372-7), bladder cancer (Fanning *et al.*, Cancer Research, 1992, 52, 1457-62), oesophageal cancer (Jankowski *et al.*, Gut, 1992, 33, 1033-8), cancer of the prostate,

- 3 -

ovarian cancer (Wiener *et al.*, Clin. Cancer Research, 1999, 5, 2164-70) and pancreatic cancer (Lutz *et al.*, Biochem. and Biophys. Res. Comm., 1998, 243, 503-8). As further human tumour tissues are tested for the Src family of non-receptor tyrosine kinases it is expected that its widespread prevalence will be established.

5 It is further known that the predominant role of c-Src non-receptor tyrosine kinase is to regulate the assembly of focal adhesion complexes through interaction with a number of cytoplasmic proteins including, for example, focal adhesion kinase and paxillin. In addition c-Src is coupled to signalling pathways that regulate the actin cytoskeleton which facilitates cell motility. Likewise, important roles are played by the c-Src, c-Yes and c-Fyn non-receptor
10 tyrosine kinases in integrin mediated signalling and in disrupting cadherin-dependent cell-cell junctions (Owens *et al.*, Molecular Biology of the Cell, 2000, 11, 51-64 and Klinghoffer *et al.*, EMBO Journal, 1999, 18, 2459-2471). Cellular motility is necessarily required for a localised tumour to progress through the stages of dissemination into the blood stream, invasion of other tissues and initiation of metastatic tumour growth. For example, colon tumour
15 progression from localised to disseminated, invasive metastatic disease has been correlated with c-Src non-receptor tyrosine kinase activity (Brunton *et al.*, Oncogene, 1997, 14, 283-293, Fincham *et al.*, EMBO J, 1998, 17, 81-92 and Verbeek *et al.*, Exp. Cell Research, 1999, 248, 531-537).

Accordingly it has been recognised that an inhibitor of such non-receptor tyrosine
20 kinases should be of value as a selective inhibitor of the motility of tumour cells and as a selective inhibitor of the dissemination and invasiveness of mammalian cancer cells leading to inhibition of metastatic tumour growth. In particular an inhibitor of such non-receptor tyrosine kinases should be of value as an anti-invasive agent for use in the containment and/or treatment of solid tumour disease.

25 We have now found that surprisingly certain quinazoline derivatives possess potent anti-tumour activity. Without wishing to imply that the compounds disclosed in the present invention possess pharmacological activity only by virtue of an effect on a single biological process, it is believed that the compounds provide an anti-tumour effect by way of inhibition of one or more of the non-receptor tyrosine-specific protein kinases that are involved in the
30 signal transduction steps which lead to the invasiveness and migratory ability of metastasising tumour cells. In particular, it is believed that the compounds of the present invention provide

- 4 -

an anti-tumour effect by way of inhibition of the Src family of non-receptor tyrosine kinases, for example by inhibition of one or more of c-Src, c-Yes and c-Fyn.

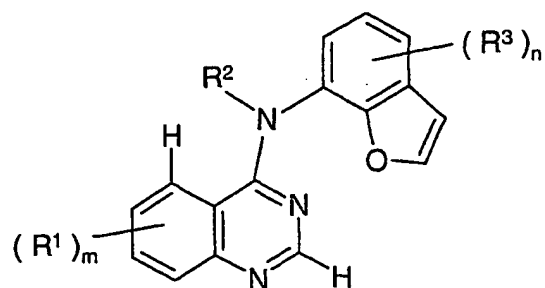
It is also known that c-Src non-receptor tyrosine kinase enzyme is involved in the control of osteoclast-driven bone resorption (Soriano *et al.*, Cell, 1991, 64, 693-702; Boyce *et al.*, J. Clin. Invest., 1992, 90, 1622-1627; Yoneda *et al.*, J. Clin. Invest., 1993, 91, 2791-2795 and Missbach *et al.*, Bone, 1999, 24, 437-49). An inhibitor of c-Src non-receptor tyrosine kinase is therefore of value in the prevention and treatment of bone diseases such as osteoporosis, Paget's disease, metastatic disease in bone and tumour-induced hypercalcaemia.

10 The compounds of the present invention are also useful in inhibiting the uncontrolled cellular proliferation which arises from various non-malignant diseases such as inflammatory diseases (for example rheumatoid arthritis and inflammatory bowel disease), fibrotic diseases (for example hepatic cirrhosis and lung fibrosis), glomerulonephritis, multiple sclerosis, psoriasis, hypersensitivity reactions of the skin, blood vessel diseases (for example
15 atherosclerosis and restenosis), allergic asthma, insulin-dependent diabetes, diabetic retinopathy and diabetic nephropathy.

Generally the compounds of the present invention possess potent inhibitory activity against the Src family of non-receptor tyrosine kinases, for example by inhibition of c-Src and/or c-Yes, whilst possessing less potent inhibitory activity against other tyrosine kinase
20 enzymes such as the receptor tyrosine kinases, for example EGF receptor tyrosine kinase and/or VEGF receptor tyrosine kinase. Furthermore, certain compounds of the present invention possess substantially better potency against the Src family of non-receptor tyrosine kinases, for example c-Src and/or c-Yes, than against VEGF receptor tyrosine kinase. Such compounds possess sufficient potency against the Src family of non-receptor tyrosine kinases,
25 for example c-Src and/or c-Yes, that they may be used in an amount sufficient to inhibit, for example, c-Src and/or c-Yes whilst demonstrating little activity against VEGF receptor tyrosine kinase.

According to one aspect of the invention there is provided a quinazoline derivative of
30 the Formula I

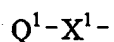
- 5 -



I

wherein m is 0, 1, 2 or 3;

each R^1 group, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, isocyano, nitro, hydroxy, mercapto, amino, formyl, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino, N-(1-6C)alkyl-(3-6C)alkynoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



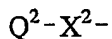
wherein X^1 is a direct bond or is selected from O, S, SO, SO₂, N(R⁴), CO, CH(OR⁴), CON(R⁴), N(R⁴)CO, SO₂N(R⁴), N(R⁴)SO₂, OC(R⁴)₂, SC(R⁴)₂ and N(R⁴)C(R⁴)₂, wherein R⁴ is hydrogen or (1-6C)alkyl, and Q¹ is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl, or (R¹)_m is (1-3C)alkylenedioxy,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO₂, N(R⁵), CO, CH(OR⁵), CON(R⁵), N(R⁵)CO, SO₂N(R⁵), N(R⁵)SO₂, CH=CH and C≡C wherein R⁵ is hydrogen or (1-6C)alkyl or, when the inserted group is N(R⁵), R⁵ may also be (2-6C)alkanoyl,

and wherein any CH₂=CH- or HC≡C- group within a R¹ substituent optionally bears at the terminal CH₂= or HC≡ position a substituent selected from halogeno, carboxy, carbamoyl, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl,

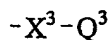
- 6 -

amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or from a group of the formula :



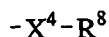
wherein X^2 is a direct bond or is selected from CO and $N(R^6)CO$, wherein R^6 is hydrogen or (1-6C)alkyl, and Q^2 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



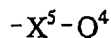
wherein X^3 is a direct bond or is selected from O, S, SO, SO_2 , $N(R^7)$, CO, $CH(OR^7)$, $CON(R^7)$, $N(R^7)CO$, $SO_2N(R^7)$, $N(R^7)SO_2$, $C(R^7)_2O$, $C(R^7)_2S$ and $N(R^7)C(R^7)_2$, wherein R^7 is hydrogen or (1-6C)alkyl, and Q^3 is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



- 7 -

wherein X^4 is a direct bond or is selected from O and $N(R^9)$, wherein R^9 is hydrogen or (1-6C)alkyl, and R^8 is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl,
 5 or from a group of the formula :



wherein X^5 is a direct bond or is selected from O, $N(R^{10})$ and CO, wherein R^{10} is hydrogen or (1-6C)alkyl, and Q^4 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same
 10 or different, selected from halogeno, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl and (1-6C)alkoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo or thioxo substituents;

R^2 is hydrogen or (1-6C)alkyl;

15 n is 0, 1, 2 or 3; and

R^3 is halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, 20 N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino, N-(1-6C)alkyl-(3-6C)alkynoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



wherein X^6 is a direct bond or is selected from O and $N(R^{12})$, wherein R^{12} is hydrogen or (1-6C)alkyl, and R^{11} is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl or di-[(1-6C)alkyl]amino-(1-6C)alkyl, or from a group of the formula :



wherein X^7 is a direct bond or is selected from O, S, SO, SO₂, $N(R^{13})$, CO, CH(OR¹³), CON(R¹³), $N(R^{13})CO$, SO₂N(R¹³), $N(R^{13})SO_2$, C(R¹³)₂O, C(R¹³)₂S and $N(R^{13})C(R^{13})_2$,

- 8 -

wherein R¹³ is hydrogen or (1-6C)alkyl, and Q⁵ is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl and (1-6C)alkoxy, and any heterocyclyl group within Q⁵ optionally bears 1 or 2 oxo or thioxo substituents, or a pharmaceutically-acceptable salt thereof.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups such as propyl, isopropyl and tert-butyl, and also (3-7C)cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. However references to individual alkyl groups such as "propyl" are specific for the straight-chain version only, references to individual branched-chain alkyl groups such as "isopropyl" are specific for the branched-chain version only and references to individual cycloalkyl groups such as "cyclopentyl" are specific for that 5-membered ring only. An analogous convention applies to other generic terms, for example (1-6C)alkoxy includes methoxy, ethoxy, cyclopropyloxy and cyclopentyloxy, (1-6C)alkylamino includes methylamino, ethylamino, cyclobutylamino and cyclohexylamino, and di-[(1-6C)alkyl]amino includes dimethylamino, diethylamino, N-cyclobutyl-N-methylamino and N-cyclohexyl-N-ethylamino.

It is to be understood that, insofar as certain of the compounds of Formula I defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the above-mentioned activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

Suitable values for the generic radicals referred to above include those set out below.

A suitable value for any one of the 'Q' groups (Q¹ to Q⁵) when it is aryl or for the aryl group within a 'Q' group is, for example, phenyl or naphthyl, preferably phenyl.

A suitable value for any one of the 'Q' groups (Q¹ or Q³) when it is (3-7C)cycloalkyl or for the (3-7C)cycloalkyl group within a 'Q' group is, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or bicyclo[2.2.1]heptyl and a

- 9 -

suitable value for any one of the 'Q' groups (Q^1 or Q^3) when it is (3-7C)cycloalkenyl or for the (3-7C)cycloalkenyl group within a 'Q' group is, for example, cyclobutenyl, cyclopentenyl, cyclohexenyl or cycloheptenyl.

A suitable value for any one of the 'Q' groups (Q^1 to Q^5) when it is heteroaryl or for
5 the heteroaryl group within a 'Q' group is, for example, an aromatic 5- or 6-membered monocyclic ring or a 9- or 10-membered bicyclic ring with up to five ring heteroatoms selected from oxygen, nitrogen and sulphur, for example furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazenyl, benzofuranyl, indolyl,
10 benzothienyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, indazolyl, benzofurazanyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl, cinnolinyl or naphthyridinyl.

A suitable value for any one of the 'Q' groups (Q^1 to Q^5) when it is heterocyclyl or for the heterocyclyl group within a 'Q' group is, for example, a non-aromatic saturated or partially saturated 3 to 10 membered monocyclic or bicyclic ring with up to five heteroatoms
15 selected from oxygen, nitrogen and sulphur, for example oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, oxepanyl, pyrrolinyl, pyrrolidinyl, morpholinyl, tetrahydro-1,4-thiazinyl, 1,1-dioxotetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl or tetrahydropyrimidinyl, preferably tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, morpholinyl,
20 1,1-dioxotetrahydro-4H-1,4-thiazinyl, piperidinyl or piperazinyl. A suitable value for such a group which bears 1 or 2 oxo or thioxo substituents is, for example, 2-oxopyrrolidinyl, 2-thioxopyrrolidinyl, 2-oxoimidazolidinyl, 2-thioxoimidazolidinyl, 2-oxopiperidinyl, 2,5-dioxopyrrolidinyl, 2,5-dioxoimidazolidinyl or 2,6-dioxopiperidinyl.

A suitable value for a 'Q' group when it is heteroaryl-(1-6C)alkyl is, for example,
25 heteroarylmethyl, 2-heteroarylethyl and 3-heteroarylpropyl. The invention comprises corresponding suitable values for 'Q' groups when, for example, rather than a heteroaryl-(1-6C)alkyl group, an aryl-(1-6C)alkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl-(1-6C)alkyl or heterocyclyl-(1-6C)alkyl group is present.

In structural Formula I there is a hydrogen atom at each of the 2- and 5-positions on
30 the quinazoline ring. It is to be understood thereby that the R^1 substituents may only be located at the 6-, 7- or 8-positions on the quinazoline ring i.e. that the 2- and 5-positions remain unsubstituted. It is further to be understood that the R^3 group that may be present on

- 10 -

the benzofuran ring within structural Formula I may be located on the phenyl ring or on the carbon atoms within the furyl ring.

Suitable values for any of the 'R' groups (R^1 to R^{13}) or for various groups within an R^1 or R^3 substituent include:-

- | | | |
|----|--|---|
| 5 | for halogeno | fluoro, chloro, bromo and iodo; |
| | for (1-6C)alkyl: | methyl, ethyl, propyl, isopropyl and <u>tert</u> -butyl; |
| | for (2-8C)alkenyl: | vinyl, isopropenyl, allyl and but-2-enyl; |
| | for (2-8C)alkynyl: | ethynyl, 2-propynyl and but-2-ynyl; |
| | for (1-6C)alkoxy: | methoxy, ethoxy, propoxy, isopropoxy and butoxy; |
| 10 | for (2-6C)alkenyloxy: | vinylloxy and allyloxy; |
| | for (2-6C)alkynyloxy: | ethynyloxy and 2-propynyloxy; |
| | for (1-6C)alkylthio: | methylthio, ethylthio and propylthio; |
| | for (1-6C)alkylsulphinyl: | methylsulphinyl and ethylsulphinyl; |
| | for (1-6C)alkylsulphonyl: | methylsulphonyl and ethylsulphonyl; |
| 15 | for (1-6C)alkylamino: | methylamino, ethylamino, propylamino, isopropylamino and butylamino; |
| | for di-[(1-6C)alkyl]amino: | dimethylamino, diethylamino, <u>N</u> -ethyl- <u>N</u> -methylamino and diisopropylamino; |
| | for (1-6C)alkoxycarbonyl: | methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and <u>tert</u> -butoxycarbonyl; |
| 20 | for <u>N</u> -(1-6C)alkylcarbamoyl: | <u>N</u> -methylcarbamoyl, <u>N</u> -ethylcarbamoyl and <u>N</u> -propylcarbamoyl; |
| | for <u>N,N</u> -di-[(1-6C)alkyl]carbamoyl: | <u>N,N</u> -dimethylcarbamoyl, <u>N</u> -ethyl- <u>N,N</u> -dimethylcarbamoyl and <u>N,N</u> -diethylcarbamoyl; |
| 25 | for (2-6C)alkanoyl: | acetyl and propionyl; |
| | for (2-6C)alkanoyloxy: | acetoxy and propionyloxy; |
| | for (2-6C)alkanoylamino: | acetamido and propionamido; |
| | for <u>N</u> -(1-6C)alkyl-(2-6C)alkanoylamino: | <u>N</u> -methylacetamido and <u>N</u> -methylpropionamido; |
| | for <u>N</u> -(1-6C)alkylsulphamoyl: | <u>N</u> -methylsulphamoyl and <u>N</u> -ethylsulphamoyl; |
| 30 | for <u>N,N</u> -di-[(1-6C)alkyl]sulphamoyl: | <u>N,N</u> -dimethylsulphamoyl; |
| | for (1-6C)alkanesulphonylamino: | methanesulphonylamino and ethanesulphonylamino; |

- 11 -

- for N-(1-6C)alkyl-(1-6C)alkanesulphonylamino: N-methylmethanesulphonylamino and
N-methylethanesulphonylamino;
- for (3-6C)alkenoylamino: acrylamido, methacrylamido and crotonamido;
- for N-(1-6C)alkyl-(3-6C)alkenoylamino: N-methylacrylamido and N-methylcrotonamido;
- 5 for (3-6C)alkynoylamino: propiolamido;
- for N-(1-6C)alkyl-(3-6C)alkynoylamino: N-methylpropiolamido;
- for amino-(1-6C)alkyl: aminomethyl, 2-aminoethyl, 1-aminoethyl and
3-aminopropyl;
- for (1-6C)alkylamino-(1-6C)alkyl: methylaminomethyl, ethylaminomethyl,
10 1-methylaminoethyl, 2-methylaminoethyl,
2-ethylaminoethyl and 3-methylaminopropyl;
- for di-[(1-6C)alkyl]amino-(1-6C)alkyl: dimethylaminomethyl, diethylaminomethyl,
1-dimethylaminoethyl, 2-dimethylaminoethyl and
3-dimethylaminopropyl;
- 15 for halogeno-(1-6C)alkyl: chloromethyl, 2-chloroethyl, 1-chloroethyl and
3-chloropropyl;
- for hydroxy-(1-6C)alkyl: hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl and
3-hydroxypropyl;
- for (1-6C)alkoxy-(1-6C)alkyl: methoxymethyl, ethoxymethyl, 1-methoxyethyl,
20 2-methoxyethyl, 2-ethoxyethyl and
3-methoxypropyl;
- for cyano-(1-6C)alkyl: cyanomethyl, 2-cyanoethyl, 1-cyanoethyl and
3-cyanopropyl;
- for (2-6C)alkanoylamino-(1-6C)alkyl: acetamidomethyl, propionamidomethyl and
25 2-acetamidoethyl; and
- for (1-6C)alkoxycarbonylamino-(1-6C)alkyl: methoxycarbonylaminomethyl,
ethoxycarbonylaminomethyl,
tert-butoxycarbonylaminomethyl and
2-methoxycarbonylaminoethyl.

30 A suitable value for $(R^1)_m$ when it is a (1-3C)alkylenedioxy group is, for example, methylenedioxy or ethylenedioxy and the oxygen atoms thereof occupy adjacent ring positions.

- 12 -

When, as defined hereinbefore, an R^1 group forms a group of the formula Q^1-X^1 - and, for example, X^1 is a $OC(R^4)_2$ linking group, it is the carbon atom, not the oxygen atom, of the $OC(R^4)_2$ linking group which is attached to the quinazoline ring and the oxygen atom is attached to the Q^1 group. Similarly, when, for example a CH_3 group within a R^1 substituent bears a group of the formula $-X^3-Q^3$ and, for example, X^3 is a $C(R^7)_2O$ linking group, it is the carbon atom, not the oxygen atom, of the $C(R^7)_2O$ linking group which is attached to the CH_3 group and the oxygen atom is linked to the Q^3 group. A similar convention applies to the attachment of the groups of the formulae Q^2-X^2 - and $-X^7-Q^5$.

As defined hereinbefore, adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent may be optionally separated by the insertion into the chain of a group such as O, $CON(R^5)$ or $C\equiv C$. For example, insertion of a $C\equiv C$ group into the ethylene chain within a 2-morpholinoethoxy group gives rise to a 4-morpholinobut-2-ynyloxy group and, for example, insertion of a CONH group into the ethylene chain within a 3-methoxypropoxy group gives rise to, for example, a 2-(2-methoxyacetamido)ethoxy group.

When, as defined hereinbefore, any $CH_2=CH-$ or $HC\equiv C-$ group within a R^1 substituent optionally bears at the terminal $CH_2=$ or $HC\equiv$ position a substituent such as a group of the formula Q^2-X^2 - wherein X^2 is, for example, $NHCO$ and Q^2 is a heterocyclyl-(1-6C)alkyl group, suitable R^1 substituents so formed include, for example, \underline{N} -[heterocyclyl-(1-6C)alkyl]carbamoylvinyl groups such as \underline{N} -(2-pyrrolidin-1-ylethyl)carbamoylvinyl or \underline{N} -[heterocyclyl-(1-6C)alkyl]carbamoylethynyl groups such as \underline{N} -(2-pyrrolidin-1-ylethyl)carbamoylethynyl.

When, as defined hereinbefore, any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents, there are suitably 1 or 2 halogeno or (1-6C)alkyl substituents present on each said CH_2 group and there are suitably 1, 2 or 3 such substituents present on each said CH_3 group.

When, as defined hereinbefore, any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group a substituent as defined hereinbefore, suitable R^1 substituents so formed include, for example, hydroxy-substituted heterocyclyl-(1-6C)alkoxy groups such as 2-hydroxy-3-piperidinopropoxy and 2-hydroxy-3-morpholinopropoxy, hydroxy-substituted amino-(2-6C)alkoxy groups such as 3-amino-2-hydroxypropoxy, hydroxy-substituted (1-6C)alkylamino-(2-6C)alkoxy groups such as 2-hydroxy-3-methylaminopropoxy, hydroxy-substituted di-[(1-6C)alkyl]amino-(2-6C)alkoxy

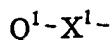
- 13 -

groups such as 3-dimethylamino-2-hydroxypropoxy, hydroxy-substituted heterocycl-
 (1-6C)alkylamino groups such as 2-hydroxy-3-piperidinopropylamino and 2-hydroxy-
 3-morpholinopropylamino, hydroxy-substituted amino-(2-6C)alkylamino groups such as
 3-amino-2-hydroxypropylamino, hydroxy-substituted (1-6C)alkylamino-(2-6C)alkylamino
 5 groups such as 2-hydroxy-3-methylaminopropylamino, hydroxy-substituted
 di-[(1-6C)alkyl]amino-(2-6C)alkylamino groups such as 3-dimethylamino-
 2-hydroxypropylamino, hydroxy-substituted (1-6C)alkoxy groups such as 2-hydroxyethoxy,
 (1-6C)alkoxy-substituted (1-6C)alkoxy groups such as 2-methoxyethoxy and
 3-ethoxypropoxy, (1-6C)alkylsulphonyl-substituted (1-6C)alkoxy groups such as
 10 2-methylsulphonylethoxy and heterocycl-yl-substituted (1-6C)alkylamino-(1-6C)alkyl groups
 such as 2-morpholinoethylaminomethyl, 2-piperazin-1-ylethylaminomethyl and
 3-morpholinopropylaminomethyl.

A suitable pharmaceutically-acceptable salt of a compound of the Formula I is, for
 example, an acid-addition salt of a compound of the Formula I, for example an acid-addition
 15 salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric,
 trifluoroacetic, citric or maleic acid; or, for example, a salt of a compound of the Formula I
 which is sufficiently acidic, for example an alkali or alkaline earth metal salt such as a
 calcium or magnesium salt, or an ammonium salt, or a salt with an organic base such as
 methylamine, dimethylamine, trimethylamine, piperidine, morpholine or
 20 tris-(2-hydroxyethyl)amine.

Particular novel compounds of the invention include, for example, quinazoline
 derivatives of the Formula I, or pharmaceutically-acceptable salts thereof, wherein, unless
 otherwise stated, each of m, R¹, R², n and R³ has any of the meanings defined hereinbefore or
 in paragraphs (a) to (h) hereinafter :-

25 (a) m is 1 or 2, and each R¹ group, which may be the same or different, is selected from
 halogeno, trifluoromethyl, hydroxy, amino, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl,
 (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino,
N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoylamino,
N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-
 30 (3-6C)alkenoylamino, (3-6C)alkynoylamino and N-(1-6C)alkyl-(3-6C)alkynoylamino,
 or from a group of the formula :



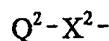
- 14 -

wherein X^1 is a direct bond or is selected from O, $N(R^4)$, $CON(R^4)$, $N(R^4)CO$ and $OC(R^4)_2$
 wherein R^4 is hydrogen or (1-6C)alkyl, and Q^1 is aryl, aryl-(1-6C)alkyl, cycloalkyl-
 (1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent
 5 are optionally separated by the insertion into the chain of a group selected from O, $N(R^5)$,
 $CON(R^5)$, $N(R^5)CO$, $CH=CH$ and $C\equiv C$ wherein R^5 is hydrogen or (1-6C)alkyl, or, when the
 inserted group is $N(R^5)$, R^5 may also be (2-6C)alkanoyl,

and wherein any $CH_2=CH-$ or $HC\equiv C-$ group within a R^1 substituent optionally bears at
 the terminal $CH_2=$ or $HC\equiv$ position a substituent selected from carbamoyl,

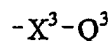
10 N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl,
 (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or from a group of the
 formula :



wherein X^2 is a direct bond or is CO or $N(R^6)CO$, wherein R^6 is hydrogen or (1-6C)alkyl, and
 15 Q^2 is heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each
 said CH_2 or CH_3 group a substituent selected from hydroxy, amino, (1-6C)alkoxy,
 (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoyloxy,
 (2-6C)alkanoylamino and N-(1-6C)alkyl-(2-6C)alkanoylamino, or from a group of the

20 formula :



wherein X^3 is a direct bond or is selected from O, $N(R^6)$, $CON(R^7)$, $N(R^7)CO$ and $C(R^7)_2O$,
 wherein R^7 is hydrogen or (1-6C)alkyl, and Q^3 is heteroaryl, heteroaryl-(1-6C)alkyl,
 heterocyclyl or heterocyclyl-(1-6C)alkyl,

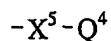
25 and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^1
 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from
 halogeno, trifluoromethyl, hydroxy, amino, carbamoyl, (1-6C)alkyl, (1-6C)alkoxy,
N-(1-6C)alkylcarbamoyl and N,N-di-[(1-6C)alkyl]carbamoyl, or optionally bears
 1 substituent selected from a group of the formula :

30 $-X^4 - R^8$

wherein X^4 is a direct bond or is selected from O and $N(R^9)$, wherein R^9 is hydrogen or
 (1-6C)alkyl, and R^8 is hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl,

- 15 -

amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl, and from a group of the formula :



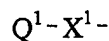
- 5 wherein X^5 is a direct bond or is selected from O, $N(R^{10})$ and CO, wherein R^{10} is hydrogen or (1-6C)alkyl, and Q^4 is heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl and (1-6C)alkoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2

10 oxo substituents;

(b) m is 1 or 2, and each R^1 group, which may be the same or different, is selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, propyl, butyl, vinyl, ethynyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, methylamino, ethylamino, propylamino, dimethylamino, diethylamino, dipropylamino, N-methylcarbamoyl,

- 15 N,N-dimethylcarbamoyl, acetamido, propionamido, acrylamido and propiolamido, or from a group of the formula :



wherein X^1 is a direct bond or is selected from O, NH, CONH, NHCO and OCH_2 and Q^1 is phenyl, benzyl, cyclopropylmethyl, 2-thienyl, 1-imidazolyl, 1,2,3-triazol-1-yl,

- 20 1,2,4-triazol-1-yl, 2-, 3- or 4-pyridyl, 2-imidazol-1-ylethyl, 3-imidazol-1-ylpropyl, 2-(1,2,3-triazolyl)ethyl, 3-(1,2,3-triazolyl)propyl, 2-(1,2,4-triazolyl)ethyl, 3-(1,2,4-triazolyl)propyl, 2-, 3- or 4-pyridylmethyl, 2-(2-, 3- or 4-pyridyl)ethyl, 3-(2-, 3- or 4-pyridyl)propyl, 1-, 2- or 3-pyrrolidinyl, morpholino, 1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl, piperidino, piperidin-3-yl, piperidin-4-yl, 1-, 3- or 4-homopiperidinyl,
- 25 piperazin-1-yl, homopiperazin-1-yl, 1-, 2- or 3-pyrrolidinylmethyl, morpholinomethyl, piperidinomethyl, 3- or 4-piperidinylmethyl, 1-, 3- or 4-homopiperidinylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-2-ylpropyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-1-ylpropyl, 4-pyrrolidin-1-ylbutyl, 2-morpholinoethyl, 3-morpholinopropyl, 4-morpholinobutyl, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethyl, 3-(1,1-dioxotetrahydro-
- 30 4H-1,4-thiazin-4-yl)propyl, 2-piperidinoethyl, 3-piperidinopropyl, 4-piperidinobutyl, 2-piperidin-3-ylethyl, 3-piperidin-3-ylpropyl, 2-piperidin-4-ylethyl, 3-piperidin-4-ylpropyl, 2-homopiperidin-1-ylethyl, 3-homopiperidin-1-ylpropyl, 2-piperazin-1-ylethyl,

- 16 -

3-piperazin-1-ylpropyl, 4-piperazin-1-ylbutyl, 2-homopiperazin-1-ylethyl or 3-homopiperazin-1-ylpropyl,

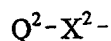
and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, NH,

5 CONH, NHCO, CH=CH and C≡C,

and wherein any CH₂=CH- or HC≡C- group within a R^1 substituent optionally bears at the terminal CH₂= or HC≡ position a substituent selected from carbamoyl,

N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl, N,N-dimethylcarbamoyl, aminomethyl, 2-aminoethyl, 3-aminopropyl, 4-aminobutyl, methylaminomethyl,

10 2-methylaminoethyl, 3-methylaminopropyl, 4-methylaminobutyl, dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl or 4-dimethylaminobutyl, or from a group of the formula :

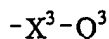


wherein X^2 is a direct bond or is CO, NHCO or N(Me)CO and Q^2 is pyridyl, pyridylmethyl,

15 2-pyridylethyl, pyrrolidin-1-yl, pyrrolidin-2-yl, morpholino, piperidino, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 4-pyrrolidin-1-ylbutyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-2-ylpropyl, morpholinomethyl, 2-morpholinoethyl, 3-morpholinopropyl, 4-morpholinobutyl, piperidinomethyl, 2-piperidinoethyl, 3-piperidinopropyl, 20 4-piperidinobutyl, piperidin-3-ylmethyl, 2-piperidin-3-ylethyl, piperidin-4-ylmethyl, 2-piperidin-4-ylethyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl or 4-piperazin-1-ylbutyl,

and wherein any CH₂ or CH₃ group within a R^1 substituent optionally bears on each said CH₂ or CH₃ group a substituent selected from hydroxy, amino, methoxy,

25 methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino, N-methyl-N-propylamino, acetoxy, acetamido and N-methylacetamido or from a group of the formula :



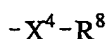
wherein X^3 is a direct bond or is selected from O, NH, CONH, NHCO and CH₂O and Q^3 is

30 pyridyl, pyridylmethyl, pyrrolidin-1-yl, pyrrolidin-2-yl, morpholino, piperidino, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-2-ylpropyl, 2-morpholinoethyl,

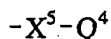
- 17 -

3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, piperidin-3-ylmethyl, 2-piperidin-3-ylethyl, piperidin-4-ylmethyl, 2-piperidin-4-ylethyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R¹ optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, methoxy, N-methylcarbamoyl and N,N-dimethylcarbamoyl, or optionally bears 1 substituent selected from a group of the formula :



wherein X⁴ is a direct bond or is selected from O and NH and R⁸ is 2-hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, cyanomethyl, aminomethyl, 2-aminoethyl, 3-aminopropyl, methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl, 2-ethylaminoethyl, 3-ethylaminopropyl, dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, acetamidomethyl, methoxycarbonylaminomethyl, ethoxycarbonylaminomethyl or tert-butoxycarbonylaminomethyl, and from a group of the formula :



wherein X⁵ is a direct bond or is selected from O, NH and CO and Q⁴ is pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, morpholinomethyl, 2-morpholinoethyl, 3-morpholinopropyl, piperidinomethyl, 2-piperidinoethyl, 3-piperidinopropyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, each of which optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy,

and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1 or 2 oxo substituents;

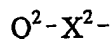
(c) m is 1 or 2 and each R¹ group, which may be the same or different, is located at the 6- and/or 7-positions and is selected from hydroxy, amino, methyl, ethyl, propyl, butyl, vinyl, ethynyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, methylamino, ethylamino, dimethylamino, diethylamino, acetamido, propionamido, cyclopentyloxy, cyclohexyloxy, phenoxy, benzyloxy, tetrahydrofuran-3-yloxy, tetrahydropyran-3-yloxy, tetrahydropyran-4-yloxy, cyclopropylmethoxy, 2-imidazol-1-ylethoxy, 3-imidazol-1-ylpropoxy, 2-(1,2,3-triazol-1-yl)ethoxy, 3-(1,2,3-triazol-1-yl)propoxy,

- 18 -

- 2-(1,2,4-triazol-1-yl)ethoxy, 3-(1,2,4-triazol-1-yl)propoxy,
 pyrid-2-ylmethoxy, pyrid-3-ylmethoxy, pyrid-4-ylmethoxy, 2-pyrid-2-ylethoxy,
 2-pyrid-3-ylethoxy, 2-pyrid-4-ylethoxy, 3-pyrid-2-ylpropoxy, 3-pyrid-3-ylpropoxy,
 3-pyrid-4-ylpropoxy, pyrrolidin-1-yl, morpholino, piperidino, piperazin-1-yl,
 5 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy,
 pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy,
 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy,
 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-
 yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy,
 10 piperidin-4-yloxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy, 2-piperidin-3-ylethoxy,
 3-piperidin-3-ylpropoxy, 2-piperidin-4-ylethoxy, 3-piperidin-4-ylpropoxy,
 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 2-piperazin-1-ylethoxy,
 3-piperazin-1-ylpropoxy, 4-piperazin-1-ylbutoxy, 2-homopiperazin-1-ylethoxy,
 3-homopiperazin-1-ylpropoxy, 2-pyrrolidin-1-ylethylamino, 3-pyrrolidin-1-ylpropylamino,
 15 4-pyrrolidin-1-ylbutylamino, pyrrolidin-3-ylamino, pyrrolidin-2-ylmethylamino, 2-pyrrolidin-
 2-ylethylamino, 3-pyrrolidin-2-ylpropylamino, 2-morpholinoethylamino,
 3-morpholinopropylamino, 4-morpholinobutylamino, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-
 4-yl)ethylamino, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propylamino,
 2-piperidinoethylamino, 3-piperidinopropylamino, 4-piperidinobutylamino,
 20 piperidin-3-ylamino, piperidin-4-ylamino, piperidin-3-ylmethylamino,
 2-piperidin-3-ylethylamino, piperidin-4-ylmethylamino, 2-piperidin-4-ylethylamino,
 2-homopiperidin-1-ylethylamino, 3-homopiperidin-1-ylpropylamino,
 2-piperazin-1-ylethylamino, 3-piperazin-1-ylpropylamino, 4-piperazin-1-ylbutylamino,
 2-homopiperazin-1-ylethylamino or 3-homopiperazin-1-ylpropylamino,
 25 and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent
 are optionally separated by the insertion into the chain of a group selected from O, NH,
 CH=CH and C≡C,
 and when R¹ is a vinyl or ethynyl group, the R¹ substituent optionally bears at the
 terminal CH₂= or HC≡ position a substituent selected from
 30 N-(2-dimethylaminoethyl)carbonyl, N-(3-dimethylaminopropyl)carbonyl,
 methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl, 4-methylaminobutyl,

- 19 -

dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl and 4-dimethylaminobutyl, or from a group of the formula :



wherein X^2 is a direct bond or is NHCO or N(Me)CO and Q^2 is imidazolylmethyl,

- 5 2-imidazolylethyl, 3-imidazolylpropyl, pyridylmethyl, 2-pyridylethyl, 3-pyridylpropyl, pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 4-pyrrolidin-1-ylbutyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-2-ylpropyl, morpholinomethyl, 2-morpholinoethyl, 3-morpholinopropyl, 4-morpholinobutyl, piperidinomethyl, 2-piperidinoethyl, 3-piperidinopropyl, 4-piperidinobutyl, piperidin-3-ylmethyl, 10 2-piperidin-3-ylethyl, piperidin-4-ylmethyl, 2-piperidin-4-ylethyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl or 4-piperazin-1-ylbutyl,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino,

- 15 N-isopropyl-N-methylamino, N-methyl-N-propylamino, acetoxy, acetamido and N-methylacetamido,

and wherein any phenyl, imidazolyl, triazolyl, pyridyl or heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl,

- 20 N-methylcarbamoyl, N,N-dimethylcarbamoyl and methoxy, and a pyrrolidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R^1 substituent is optionally N-substituted with 2-methoxyethyl, 3-methoxypropyl, cyanomethyl, 2-aminoethyl, 3-aminopropyl, 2-methylaminoethyl, 3-methylaminopropyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, 2-pyrrolidin-1-ylethyl, 25 3-pyrrolidin-1-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, the last 8 of which substituents each optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy,

- and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2
30 oxo substituents;

(d) m is 1 and the R^1 group is located at the 6- or 7-position and is selected from hydroxy, amino, methyl, ethyl, propyl, butyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy,

- 20 -

- methyamino, ethyamino, dimethyamino, diethyamino, acetamido, propionamido, benzyloxy, 2-imidazol-1-ylethoxy, 2-(1,2,3-triazol-1-yl)ethoxy, 2-(1,2,4-triazol-1-yl)ethoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy,
- 5 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, 2-piperidin-3-ylethoxy, piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy,
- 10 3-homopiperidin-1-ylpropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy or 3-homopiperazin-1-ylpropoxy,
- and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O, NH, CH=CH and C≡C,
- 15 and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each said CH₂ or CH₃ group a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, methyamino, dimethyamino, diisopropylamino, N-ethyl-N-methyamino, N-isopropyl-N-methyamino and acetoxy,
- and wherein any heteroaryl or heterocyclyl group within a substituent on R¹ optionally
- 20 bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, ethyl and methoxy,
- and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1 or 2 oxo substituents;
- (e) R² is hydrogen;
- 25 (f) n is 1 or 2 and the R³ groups, which may be the same or different, are located at the 5- and/or 6-positions of the benzofuran ring and are selected from halogeno, trifluoromethyl, cyano, hydroxy, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl and (1-6C)alkoxy;
- (g) n is 1 or 2 and the R³ groups, which may be the same or different, are located at the 5- and/or 6-positions of the benzofuran ring and are selected from fluoro, chloro, bromo, iodo,
- 30 trifluoromethyl, cyano, hydroxy, methyl, ethyl, vinyl, allyl, isopropenyl, ethynyl, 1-propynyl, 2-propynyl, methoxy and ethoxy; and
- (h) n is 0.

- 21 -

A preferred compound of the invention is a quinazoline derivative of the Formula I wherein :

m is 1 or 2 and each R¹ group, which may be the same or different, is located at the 6- and/or 7-positions and is selected from hydroxy, amino, methyl, ethyl, propyl, butyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, methylamino, ethylamino, dimethylamino, diethylamino, acetamido, propionamido, 2-imidazol-1-ylethoxy, 2-(1,2,4-triazol-1-yl)ethoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy, 2-piperidin-3-ylethoxy, 3-piperidin-3-ylpropoxy, 2-piperidin-4-ylethoxy, 3-piperidin-4-ylpropoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 4-piperazin-1-ylbutoxy, 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O, NH, CH=CH and C≡C,

and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each said CH₂ or CH₃ group a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diethylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino, N-methyl-N-propylamino and acetoxy;

and wherein any heteroaryl or heterocyclyl group within a substituent on R¹ optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, methoxy, N-methylcarbamoyl and N,N-dimethylcarbamoyl and a pyrrolidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R¹ substituent is optionally N-substituted with 2-methoxyethyl, 3-methoxypropyl, cyanomethyl, 2-aminoethyl, 3-aminopropyl, 2-methylaminoethyl, 3-methylaminopropyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-piperazin-1-ylethyl or

- 22 -

3-piperazin-1-ylpropyl, the last 8 of which substituents each optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy,

and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1 or 2

5 oxo substituents;

R² is hydrogen;

n is 0 or 1 and the R³ group, if present, is located at the 5- or 6-position of the benzofuran ring and is selected from fluoro, chloro, trifluoromethyl, cyano, hydroxy, methyl, ethyl, vinyl, allyl, ethynyl, methoxy and ethoxy;

10 or a pharmaceutically-acceptable acid-addition salt thereof.

A further preferred compound of the invention is a quinazoline derivative of the Formula I wherein :

m is 2 and the first R¹ group is located at the 6-position and is selected from hydroxy, methoxy, ethoxy and propoxy, and the second R¹ group is located at the 7-position and is
 15 selected from 2-dimethylaminoethoxy, 3-dimethylaminopropoxy, 4-dimethylaminobutoxy, 2-diethylaminoethoxy, 3-diethylaminopropoxy, 4-diethylaminobutoxy, 2-diisopropylaminoethoxy, 3-diisopropylaminopropoxy, 4-diisopropylaminobutoxy, 2-(N-isopropyl-N-methylamino)ethoxy, 3-(N-isopropyl-N-methylamino)propoxy, 4-(N-isopropyl-N-methylamino)butoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy,
 20 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, N-methylpyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy,
 25 piperidin-3-yloxy, N-methylpiperidin-3-yloxy, piperidin-4-yloxy, N-methylpiperidin-4-yloxy, piperidin-3-ylmethoxy, N-methylpiperidin-3-ylmethoxy, piperidin-4-ylmethoxy, N-methylpiperidin-4-ylmethoxy, 2-piperidin-3-ylethoxy, 2-(N-methylpiperidin-3-yl)ethoxy, 3-piperidin-3-ylpropoxy, 3-(N-methylpiperidin-3-yl)propoxy, 2-piperidin-4-ylethoxy, 2-(N-methylpiperidin-4-yl)ethoxy, 3-piperidin-4-ylpropoxy,
 30 3-(N-methylpiperidin-4-yl)propoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 4-(4-methylpiperazin-1-yl)butoxy, 2-(4-cyanomethylpiperazin-1-yl)ethoxy, 3-(4-cyanomethylpiperazin-1-yl)propoxy,

- 23 -

4-(4-cyanomethylpiperazin-1-yl)butoxy, 2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy,
2-methylsulphonylethoxy and 3-methylsulphonylpropoxy,

and wherein any CH₂ group within the second R¹ group that is attached to two carbon atoms optionally bears a hydroxy group or acetoxy group on said CH₂ group,

5 and wherein any heterocyclyl group within the second R¹ group optionally bears 1 or 2 oxo substituents;

R² is hydrogen; and

n is 0 or n is 1 and the R³ group is located at the 5- or 6-position of the benzofuran ring and is selected from fluoro, chloro, trifluoromethyl, cyano, methyl, ethyl, ethynyl, methoxy
10 and ethoxy;
or a pharmaceutically-acceptable acid-addition salt thereof.

A further preferred compound of the invention is a quinazoline derivative of the Formula I wherein :

m is 2 and the first R¹ group is located at the 6-position and is selected from hydroxy,
15 methoxy, ethoxy and propoxy, and the second R¹ group is located at the 7-position and is selected from 2-dimethylaminoethoxy, 3-dimethylaminopropoxy, 2-diethylaminoethoxy, 3-diethylaminopropoxy, 2-diisopropylaminoethoxy, 3-diisopropylaminopropoxy, 2-(N-isopropyl-N-methylamino)ethoxy, 3-(N-isopropyl-N-methylamino)propoxy, 2-(N-isobutyl-N-methylamino)ethoxy, 3-(N-isobutyl-N-methylamino)propoxy,
20 2-(N-allyl-N-methylamino)ethoxy, 3-(N-allyl-N-methylamino)propoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, piperidin-3-ylmethoxy,
25 N-methylpiperidin-3-ylmethoxy, piperidin-4-ylmethoxy, N-methylpiperidin-4-ylmethoxy, 2-piperidin-3-ylethoxy, 2-(N-methylpiperidin-3-yl)ethoxy, 3-piperidin-3-ylpropoxy, 3-(N-methylpiperidin-3-yl)propoxy, 2-piperidin-4-ylethoxy, 2-(N-methylpiperidin-4-yl)ethoxy, 3-piperidin-4-ylpropoxy, 3-(N-methylpiperidin-4-yl)propoxy, 3-homopiperidinopropoxy,
30 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 2-(4-cyanomethylpiperazin-1-yl)ethoxy and 3-(4-cyanomethylpiperazin-1-yl)propoxy,

- 24 -

and wherein any CH₂ group within the second R¹ group that is attached to two carbon atoms optionally bears a hydroxy group or acetoxy group on said CH₂ group,

R² is hydrogen; and

n is 0 or n is 1 or 2 and an R³ group, if present, is located at the 5- or 6-position of the benzofuran ring and is selected from fluoro, chloro, bromo, trifluoromethyl, cyano, methyl, ethyl, ethynyl, methoxy and ethoxy;
or a pharmaceutically-acceptable acid-addition salt thereof.

A further preferred compound of the invention is a quinazoline derivative of the Formula I wherein :

10 m is 2 and the first R¹ group is a 6-methoxy group and the second R¹ group is located at the 7-position and is selected from 3-(N-isopropyl-N-methylamino)propoxy, 3-(N-isobutyl-N-methylamino)propoxy, 3-pyrrolidin-1-ylpropoxy, 3-morpholinopropoxy, 3-piperidinopropoxy, piperidin-4-ylmethoxy, N-methylpiperidin-4-ylmethoxy, 3-homopiperidinopropoxy, 2-(4-methylpiperazin-1-yl)ethoxy,
15 3-(4-methylpiperazin-1-yl)propoxy and 3-(4-cyanomethylpiperazin-1-yl)propoxy,

and wherein any CH₂ group within the second R¹ group that is attached to two carbon atoms optionally bears a hydroxy group or acetoxy group on said CH₂ group;

R² is hydrogen; and

n is 0 or n is 1 and the R³ group is located at the 5- or 6-position of the benzofuran ring
20 and is selected from fluoro and chloro;
or a pharmaceutically-acceptable acid-addition salt thereof.

A further preferred compound of the invention is a quinazoline derivative of the Formula I wherein :

m is 2 and the first R¹ group is a 6-methoxy group and the second R¹ group is located
25 at the 7-position and is selected from 3-(N-isopropyl-N-methylamino)propoxy, 3-pyrrolidin-1-ylpropoxy, 3-morpholinopropoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 3-piperidinopropoxy, N-methylpiperidin-4-ylmethoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 3-(4-cyanomethylpiperazin-1-yl)propoxy and 2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy,

30 and wherein any CH₂ group within the second R¹ group that is attached to two carbon atoms optionally bears a hydroxy group on said CH₂ group;

R² is hydrogen; and

- 25 -

n is 0;

or a pharmaceutically-acceptable acid-addition salt thereof.

A particular preferred compound of the invention is, for example, a quinazoline derivative of the Formula I selected from :-

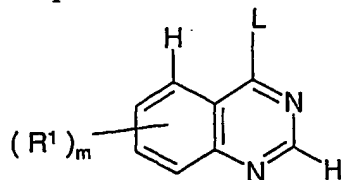
- 5 4-(7-benzofuranylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
- 4-(7-benzofuranylamino)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,
- 4-(7-benzofuranylamino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,
- 4-(7-benzofuranylamino)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,
- 4-(3-chlorobenzofuran-7-ylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
- 10 4-(3-chlorobenzofuran-7-ylamino)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,
- 4-(3-chlorobenzofuran-7-ylamino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,
- 4-(3-chlorobenzofuran-7-ylamino)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,
- 4-(6-chlorobenzofuran-7-ylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
- 15 4-(6-chlorobenzofuran-7-ylamino)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,
- 4-(6-chlorobenzofuran-7-ylamino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,
- 4-(6-chlorobenzofuran-7-ylamino)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,
- 4-(5-fluorobenzofuran-7-ylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
- 20 4-(5-fluorobenzofuran-7-ylamino)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,
- 4-(5-fluorobenzofuran-7-ylamino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,
- 4-(5-fluorobenzofuran-7-ylamino)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,
- 4-(7-benzofuranylamino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline,
- 25 7-(2-acetoxy-3-pyrrolidin-1-ylpropoxy)-4-(3-chlorobenzofuran-7-ylamino)-6-methoxyquinazoline,
- 7-[2-acetoxy-3-(N-isopropyl-N-methylamino)propoxy]-4-(3-chlorobenzofuran-7-ylamino)-6-methoxyquinazoline,
- 7-[2-acetoxy-3-(4-cyanomethylpiperazin-1-yl)propoxy]-4-(3-chlorobenzofuran-7-ylamino)-
- 30 6-methoxyquinazoline,
- 7-(2-acetoxy-3-piperidinopropoxy)-4-(3-chlorobenzofuran-7-ylamino)-6-methoxyquinazoline,

- 26 -

- 4-(3-chlorobenzofuran-7-ylamino)-7-(2-hydroxy-3-pyrrolidin-1-ylpropoxy)-
 6-methoxyquinazoline,
 4-(3-chlorobenzofuran-7-ylamino)-7-[2-hydroxy-3-(N-isopropyl-N-methylamino)propoxy]-
 6-methoxyquinazoline,
 5 4-(3-chlorobenzofuran-7-ylamino)-7-[3-(4-cyanomethylpiperazin-1-yl)-2-hydroxypropoxy]-
 6-methoxyquinazoline and
 4-(3-chlorobenzofuran-7-ylamino)-7-(2-hydroxy-3-piperidinopropoxy)-
 6-methoxyquinazoline;
 or a pharmaceutically-acceptable acid-addition salt thereof.

- 10 A quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes, when used to prepare a quinazoline derivative of the Formula I are provided as a further feature of the invention and are illustrated by the following representative process variants in which, unless otherwise stated, m, R¹, R², n
 15 and R³ have any of the meanings defined hereinbefore. Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described in conjunction with the following representative process variants and within the accompanying Examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic
 20 chemist.

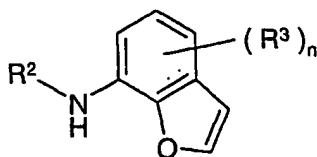
- (a) The reaction of a quinazoline of the Formula II



II

wherein L is a displaceable group and m and R¹ have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with an aniline of the

- 25 Formula III



III

- 27 -

wherein R^2 , n and R^3 have any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

The reaction may conveniently be carried out in the presence of a suitable acid or in the presence of a suitable base. A suitable acid is, for example, an inorganic acid such as, for example, hydrogen chloride or hydrogen bromide. A suitable base is, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or, for example, an alkali or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide, or, for example, an alkali metal hydride, for example sodium hydride, or, for example, an alkali metal amide, for example sodium amide or sodium 1,1,1,3,3,3-hexamethyldisilazide.

A suitable displaceable group L is, for example, a halogeno, alkoxy, aryloxy or sulphonyloxy group, for example a chloro, bromo, methoxy, phenoxy, pentafluorophenoxy, methanesulphonyloxy or toluene-4-sulphonyloxy group. The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example an alcohol or ester such as methanol, ethanol, isopropanol or ethyl acetate, a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxan, an aromatic solvent such as toluene, or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulphoxide. The reaction is conveniently carried out at a temperature in the range, for example, 10 to 250°C, preferably in the range 40 to 120°C.

Typically, the quinazoline of the Formula II may be reacted with an aniline of the Formula III in the presence of a protic solvent such as isopropanol, conveniently in the presence of an acid, for example hydrogen chloride gas in diethyl ether, and at a temperature in the range, for example, 25 to 150°C, preferably at or near the reflux temperature of the reaction solvent.

The quinazoline derivative of the Formula I may be obtained from this process in the form of the free base or alternatively it may be obtained in the form of a salt with the acid of the formula H-L wherein L has the meaning defined hereinbefore. When it is desired to obtain the free base from the salt, the salt may be treated with a suitable base, for example, an

- 28 -

organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or, for example, an alkali or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium
5 hydroxide or potassium hydroxide.

Protecting groups may in general be chosen from any of the groups described in the literature or known to the skilled chemist as appropriate for the protection of the group in question and may be introduced by conventional methods. Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as
10 appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower", as in, for example, lower alkyl, signifies that the group to which it is applied
15 preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned are, of course, within the scope of the invention.

A carboxy protecting group may be the residue of an ester-forming aliphatic or
20 arylaliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1-20 carbon atoms). Examples of carboxy protecting groups include straight or branched chain (1-12C)alkyl groups (for example isopropyl, and tert-butyl); lower alkoxy- lower alkyl groups (for example methoxymethyl, ethoxymethyl and isobutoxymethyl); lower acyloxy-lower alkyl groups, (for example acetoxymethyl,
25 propionyloxymethyl, butyryloxymethyl and pivaloyloxymethyl); lower alkoxycarbonyloxy-lower alkyl groups (for example 1-methoxycarbonyloxyethyl and 1-ethoxycarbonyloxyethyl); aryl-lower alkyl groups (for example benzyl, 4-methoxybenzyl, 2-nitrobenzyl, 4-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (for example trimethylsilyl and tert-butyldimethylsilyl); tri(lower alkyl)silyl-lower alkyl groups
30 (for example trimethylsilylethyl); and (2-6C)alkenyl groups (for example allyl). Methods particularly appropriate for the removal of carboxyl protecting groups include for example acid-, base-, metal- or enzymically-catalysed cleavage.

- 29 -

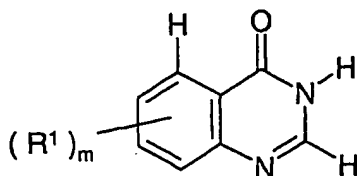
Examples of hydroxy protecting groups include lower alkyl groups (for example tert-butyl), lower alkenyl groups (for example allyl); lower alkanoyl groups (for example acetyl); lower alkoxy carbonyl groups (for example tert-butoxycarbonyl); lower alkenyloxycarbonyl groups (for example allyloxycarbonyl); aryl-lower alkoxy carbonyl groups (for example benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl); tri(lower alkyl)silyl (for example trimethylsilyl and tert-butyldimethylsilyl) and aryl-lower alkyl (for example benzyl) groups.

Examples of amino protecting groups include formyl, aryl-lower alkyl groups (for example benzyl and substituted benzyl, 4-methoxybenzyl, 2-nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-4-anisylmethyl and furylmethyl groups; lower alkoxy carbonyl (for example tert-butoxycarbonyl); lower alkenyloxycarbonyl (for example allyloxycarbonyl); aryl-lower alkoxy carbonyl groups (for example benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl); trialkylsilyl (for example trimethylsilyl and tert-butyldimethylsilyl); alkylidene (for example methylidene) and benzylidene and substituted benzylidene groups.

Methods appropriate for removal of hydroxy and amino protecting groups include, for example, acid-, base-, metal- or enzymically-catalysed hydrolysis for groups such as 2-nitrobenzyloxycarbonyl, hydrogenation for groups such as benzyl and photolytically for groups such as 2-nitrobenzyloxycarbonyl.

The reader is referred to Advanced Organic Chemistry, 4th Edition, by J. March, published by John Wiley & Sons 1992, for general guidance on reaction conditions and reagents and to Protective Groups in Organic Synthesis, 2nd Edition, by T. Green *et al.*, also published by John Wiley & Son, for general guidance on protecting groups.

Quinazoline starting materials of the Formula II may be obtained by conventional procedures. For example, a 3,4-dihydroquinazolin-4-one of Formula IV



IV

wherein *m* and *R*¹ have any of the meanings defined hereinbefore except that any functional group is protected if necessary, may be reacted with a halogenating agent such as thionyl

- 30 -

chloride, phosphoryl chloride or a mixture of carbon tetrachloride and triphenylphosphine whereafter any protecting group that is present is removed by conventional means.

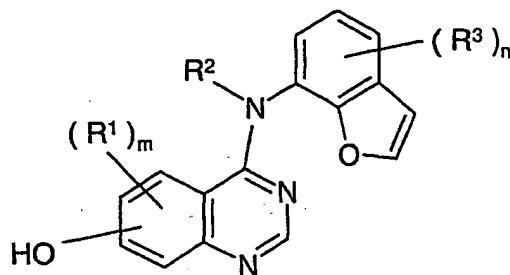
The 4-chloroquinazoline so obtained may be converted, if required, into a 4-pentafluorophenoxyquinazoline by reaction with pentafluorophenol in the presence of a suitable base such as potassium carbonate and in the presence of a suitable solvent such as N,N-dimethylformamide.

7-Aminobenzofuran starting materials of the Formula III may be obtained by conventional procedures as illustrated in the Examples.

(b) For the production of those compounds of the Formula I wherein at least one R¹ group is a group of the formula



wherein Q¹ is an aryl-(1-6C)alkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl-(1-6C)alkyl or heterocyclyl-(1-6C)alkyl group or an optionally substituted alkyl group and X¹ is an oxygen atom, the coupling, conveniently in the presence of a suitable dehydrating agent, of a quinazoline of the Formula V



V

wherein m, R¹, R², n and R³ have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with an appropriate alcohol wherein any functional group is protected if necessary whereafter any protecting group that is present is removed by conventional means.

A suitable dehydrating agent is, for example, a carbodiimide reagent such as dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or a mixture of an azo compound such as diethyl or di-tert-butyl azodicarboxylate and a phosphine such as triphenylphosphine. The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example a halogenated solvent such as methylene chloride, chloroform

- 31 -

or carbon tetrachloride and at a temperature in the range, for example, 10 to 150°C, preferably at or near ambient temperature.

The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride and at a temperature in the range, for example, 10 to 150°C, preferably at or near ambient temperature.

(c) For the production of those compounds of the Formula I wherein an R^1 group contains a primary or secondary amino group, the cleavage of the corresponding compound of the Formula I wherein the R^1 group contains a protected primary or secondary amino group.

10 Suitable protecting groups for an amino group are, for example, any of the protecting groups disclosed hereinbefore for an amino group. Suitable methods for the cleavage of such amino protecting groups are also disclosed hereinbefore. In particular, a suitable protecting group is a lower alkoxycarbonyl group such as a tert-butoxycarbonyl group which may be cleaved under conventional reaction conditions such as under acid-catalysed hydrolysis, for example in the presence of trifluoroacetic acid.

(d) For the production of those compounds of the Formula I wherein an R^1 group contains a (1-6C)alkoxy or substituted (1-6C)alkoxy group or a (1-6C)alkylamino or substituted (1-6C)alkylamino group, the alkylation, conveniently in the presence of a suitable base as defined hereinbefore, of a quinazoline derivative of the formula I wherein the R^1 group contains a hydroxy group or a primary or secondary amino group as appropriate.

20 A suitable alkylating agent is, for example, any agent known in the art for the alkylation of hydroxy to alkoxy or substituted alkoxy, or for the alkylation of amino to alkylamino or substituted alkylamino, for example an alkyl or substituted alkyl halide, for example a (1-6C)alkyl chloride, bromide or iodide or a substituted (1-6C)alkyl chloride, bromide or iodide, conveniently in the presence of a suitable base as defined hereinbefore, in a suitable inert solvent or diluent as defined hereinbefore and at a temperature in the range, for example, 10 to 140°C, conveniently at or near ambient temperature.

Conveniently for the production of those compounds of the Formula I wherein R^1 contains a (1-6C)alkylamino or substituted (1-6C)alkylamino group, a reductive amination reaction may be employed. For example, for the production of those compounds of the Formula I wherein R^1 contains a N-methyl group, the corresponding compound containing a N-H group may be reacted with formaldehyde in the presence of a suitable reducing agent. A

- 32 -

suitable reducing agent is, for example, a hydride reducing agent, for example an alkali metal aluminium hydride such as lithium aluminium hydride or, preferably, an alkali metal borohydride such as sodium borohydride, sodium cyanoborohydride, sodium triethylborohydride, sodium trimethoxyborohydride and sodium triacetoxymethylborohydride. The reaction is conveniently performed in a suitable inert solvent or diluent, for example tetrahydrofuran and diethyl ether for the more powerful reducing agents such as lithium aluminium hydride, and, for example, methylene chloride or a protic solvent such as methanol and ethanol for the less powerful reducing agents such as sodium triacetoxymethylborohydride and sodium cyanoborohydride. The reaction is performed at a temperature in the range, for example, 10 to 80°C, conveniently at or near ambient temperature.

(e) For the production of those compounds of the Formula I wherein R^1 is an amino-hydroxy-disubstituted (1-6C)alkoxy group (such as 2-hydroxy-3-pyrrolidin-1-ylpropoxy or 3-[N-allyl-N-methylamino]-2-hydroxypropoxy), the reaction of a compound of the Formula I wherein the R^1 group contains an epoxy-substituted (1-6C)alkoxy group with a heterocyclyl compound or an appropriate amine.

The reaction is conveniently carried out in the presence of a suitable inert diluent or carrier as defined hereinbefore and at a temperature in the range 10 to 150°C, preferably at or near ambient temperature.

(f) For the production of those compounds of the Formula I wherein an R^1 group contains a hydroxy group, the cleavage of the corresponding compound of the Formula I wherein the R^1 group contains a protected hydroxy group.

Suitable protecting groups for a hydroxy group are, for example, any of the protecting groups disclosed hereinbefore. Suitable methods for the cleavage of such hydroxy protecting groups are also disclosed hereinbefore. In particular, a suitable protecting group is a lower alkanoyl group such as an acetyl group which may be cleaved under conventional reaction conditions such as under base-catalysed conditions, for example in the presence of ammonia.

When a pharmaceutically-acceptable salt of a quinazoline derivative of the Formula I is required, for example an acid-addition salt, it may be obtained by, for example, reaction of said quinazoline derivative with a suitable acid using a conventional procedure.

- 33 -

Biological Assays

The following assays can be used to measure the effects of the compounds of the present invention as c-Src tyrosine kinase inhibitors, as inhibitors in vitro of the proliferation of c-Src transfected fibroblast cells, as inhibitors in vitro of the migration of A549 human lung
5 tumour cells and as inhibitors in vivo of the growth in nude mice of xenografts of A549 tissue.

(a) In Vitro Enzyme Assay

The ability of test compounds to inhibit the phosphorylation of a tyrosine containing polypeptide substrate by the enzyme c-Src kinase was assessed using a conventional Elisa assay.

10 A substrate solution [100µl of a 20µg/ml solution of the polyamino acid Poly(Glu, Tyr) 4:1 (Sigma Catalogue No. P0275) in phosphate buffered saline (PBS) containing 0.2mg/ml of sodium azide] was added to each well of a number of Nunc 96-well immunoplates (Catalogue No. 439454) and the plates were sealed and stored at 4°C for 16 hours. The excess of substrate solution was discarded, and aliquots of Bovine Serum
15 Albumin (BSA; 150µl of a 5% solution in PBS) were transferred into each substrate-coated assay well and incubated for 1 hour at ambient temperature to block non specific binding. The assay plate wells were washed in turn with PBS containing 0.05% v/v Tween 20 (PBST) and with Hepes pH7.4 buffer (50mM, 300µl/well) before being blotted dry.

Each test compound was dissolved in dimethyl sulphoxide and diluted with distilled
20 water to give a series of dilutions (from 100µM to 0.001µM). Portions (25µl) of each dilution of test compound were transferred to wells in the washed assay plates. "Total" control wells contained diluted DMSO instead of compound. Aliquots (25µl) of an aqueous magnesium chloride solution (80mM) containing adenosine-5'-triphosphate (ATP; 40µM) was added to all test wells except the "blank" control wells which contained magnesium chloride without
25 ATP.

Active human c-Src kinase (recombinant enzyme expressed in Sf9 insect cells; obtained from Upstate Biotechnology Inc. product 14-117) was diluted immediately prior to use by a factor of 1:10,000 with an enzyme diluent which comprised 100mM Hepes pH7.4 buffer, 0.2mM sodium orthovanadate, 2mM dithiothreitol and 0.02% BSA. To start the
30 reactions, aliquots (50µl) of freshly diluted enzyme were added to each well and the plates were incubated at ambient temperature for 20 minutes. The supernatant liquid in each well was discarded and the wells were washed twice with PBST. Mouse IgG anti-phosphotyrosine

- 34 -

antibody (Upstate Biotechnology Inc. product 05-321; 100µl) was diluted by a factor of 1:6000 with PBST containing 0.5% w/v BSA and added to each well. The plates were incubated for 1 hour at ambient temperature. The supernatant liquid was discarded and each well was washed with PBST (x4). Horse radish peroxidase (HRP)-linked sheep anti-mouse
5 Ig antibody (Amersham Catalogue No. NXA 931; 100µl) was diluted by a factor of 1:500 with PBST containing 0.5% w/v BSA and added to each well. The plates were incubated for 1 hour at ambient temperature. The supernatant liquid was discarded and the wells were washed with PBST (x4).

A PCSB capsule (Sigma Catalogue No. P4922) was dissolved in distilled water
10 (100ml) to provide phosphate-citrate pH5 buffer (50mM) containing 0.03% sodium perborate. An aliquot (50ml) of this buffer was mixed with a 50mg tablet of 2,2'-azinobis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS; Boehringer Catalogue No. 1204 521). Aliquots (100µl) of the resultant solution were added to each well. The plates were incubated for 20 to 60 minutes at ambient temperature until the optical density value of
15 the "total" control wells, measured at 405nm using a plate reading spectrophotometer, was approximately 1.0. "Blank" (no ATP) and "total" (no compound) control values were used to determine the dilution range of test compound which gave 50% inhibition of enzyme activity.

(b) In Vitro c-Src transfected NIH 3T3 (c-src 3T3) Fibroblast Proliferation Assay

This assay determined the ability of a test compound to inhibit the proliferation of
20 National Institute of Health (NIH) mouse 3T3 fibroblast cells that had been stably-transfected with an activating mutant (Y530F) of human c-Src.

Using a similar procedure to that described by Shalloway *et al.*, Cell, 1987, 49, 65-73, NIH 3T3 cells were transfected with an activating mutant (Y530F) of human c-Src. The resultant c-Src 3T3 cells were typically seeded at 1.5×10^4 cells per well into 96-well tissue-
25 culture-treated clear assay plates (Costar) each containing an assay medium comprising Dulbecco's modified Eagle's medium (DMEM; Sigma) plus 0.5% foetal calf serum (FCS), 2mM glutamine, 100 units/ml penicillin and 0.1mg/ml streptomycin in 0.9% aqueous sodium chloride solution. The plates were incubated overnight at 37°C in a humidified (7.5% CO₂ : 95% air) incubator.

30 Test compounds were solubilised in DMSO to form a 10mM stock solution. Aliquots of the stock solution were diluted with the DMEM medium described above and added to appropriate wells. Serial dilutions were made to give a range of test concentrations. Control

- 35 -

wells to which test compound was not added were included on each plate. The plates were incubated overnight at 37°C in a humidified (7.5% CO₂ : 95% air) incubator.

BrdU labelling reagent (Boehringer Mannheim Catalogue No. 647 229) was diluted by a factor of 1:100 in DMEM medium containing 0.5% FCS and aliquots (20µl) were added to each well to give a final concentration of 10µM). The plates were incubated at 37°C for 2 hours. The medium was decanted. A denaturing solution (FixDenat solution, Boehringer Mannheim Catalogue No. 647 229; 50µl) was added to each well and the plates were placed on a plate shaker at ambient temperature for 45 minutes. The supernatant was decanted and the wells were washed with PBS (200µl per well). Anti-BrdU-Peroxidase solution (Boehringer Mannheim Catalogue No. 647 229) was diluted by a factor of 1:100 in PBS containing 1% BSA and 0.025% dried skimmed milk (Marvel (registered trade mark), Premier Beverages, Stafford, GB) and an aliquot (100µl) of the resultant solution was added to each well. The plates were placed on a plate shaker at ambient temperature for 90 minutes. The wells were washed with PBS (x5) to ensure removal of non bound antibody conjugate. The plates were blotted dry and tetramethylbenzidine substrate solution (Boehringer Mannheim Catalogue No. 647 229; 100µl) was added to each well. The plates were gently agitated on a plate shaker while the colour developed during a 10 to 20 minute period. The absorbance of the wells was measured at 690nm. The extent of inhibition of cellular proliferation at a range of concentrations of each test compound was determined and an anti-proliferative IC₅₀ value was derived.

(c) In Vitro Microdroplet Migration Assay

This assay determines the ability of a test compound to inhibit the migration of adherent mammalian cell lines, for example the human tumour cell line A549.

RPMI medium(Sigma) containing 10% FCS, 1% L-glutamine and 0.3% agarose

- 36 -

gelling of the agarose-containing droplets. Aliquots (90 μ l) of medium which had been cooled to 4°C were transferred into each well, taking care not to disturb the microdroplets. Test compounds were diluted from a 10mM stock solution in DMSO using RPMI medium as described above. Aliquots (10 μ l) of the diluted test compounds were transferred to the wells, again taking care not to disturb the microdroplets. The plates were incubated at 37°C in a humidified (7.5% CO₂ : 95% air) incubator for about 48 hours.

Migration was assessed visually and the distance of migration was measured back to the edge of the agar droplet. A migratory inhibitory IC₅₀ was derived by plotting the mean migration measurement against test compound concentration.

10 (d) In Vivo A549 Xenograft Growth Assay

This test measures the ability of compounds to inhibit the growth of the A549 human carcinoma grown as a tumour in athymic nude mice (Alderley Park nu/nu strain). A total of about 5 x 10⁶ A549 cells in matrigel (Beckton Dickinson Catalogue No. 40234) were injected subcutaneously into the left flank of each test mouse and the resultant tumours were allowed to grow for about 14 days. Tumour size was measured twice weekly using callipers and a theoretical volume was calculated. Animals were selected to provide control and treatment groups of approximately equal average tumour volume. Test compounds were prepared as a ball-milled suspension in 1% polysorbate vehicle and dosed orally once daily for a period of about 28 days. The effect on tumour growth was assessed.

20 Although the pharmacological properties of the compounds of the Formula I vary with structural change as expected, in general activity possessed by compounds of the Formula I, may be demonstrated at the following concentrations or doses in one or more of the above tests (a), (b), (c) and (d):-

- 25 Test (a):- IC₅₀ in the range, for example, 0.001 - 10 μ M;
Test (b):- IC₅₀ in the range, for example, 0.01 - 20 μ M;
Test (c):- activity in the range, for example, 0.01-25 μ M;
Test (d):- activity in the range, for example, 1-200 mg/kg/day.

No physiologically-unacceptable toxicity was observed in Test (d) at the effective dose for compounds tested of the present invention. Accordingly no untoward toxicological effects are expected when a compound of Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore is administered at the dosage ranges defined hereinafter.

- 37 -

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

5 The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for
10 example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended
15 for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral
20 administration to humans will generally contain, for example, from 0.5 mg to 0.5 g of active agent (more suitably from 0.5 to 100 mg, for example from 1 to 30 mg) compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition.

The size of the dose for therapeutic or prophylactic purposes of a compound of the
25 Formula I will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

In using a compound of the Formula I for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.1 mg/kg to
30 75 mg/kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.1 mg/kg to 30 mg/kg body weight will

- 38 -

generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.05 mg/kg to 25 mg/kg body weight will be used. Oral administration is however preferred, particularly in tablet form. Typically, unit dosage forms will contain about 0.5 mg to 0.5 g of a compound of this invention.

5 According to a further aspect of the invention there is provided a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

As stated above, it is known that the predominant role of c-Src non-receptor tyrosine kinase is to regulate cell motility which is necessarily required for a localised tumour to
10 progress through the stages of dissemination into the blood stream, invasion of other tissues and initiation of metastatic tumour growth. We have found that the quinazoline derivatives of the present invention possess potent anti-tumour activity which it is believed is obtained by way of inhibition of one or more of the non-receptor tyrosine-specific protein kinases such as c-Src kinase that are involved in the signal transduction steps which lead to the invasiveness
15 and migratory ability of metastasising tumour cells.

Accordingly the quinazoline derivatives of the present invention are of value as anti-tumour agents, in particular as selective inhibitors of the motility, dissemination and invasiveness of mammalian cancer cells leading to inhibition of metastatic tumour growth. Particularly, the quinazoline derivatives of the present invention are of value as anti-invasive
20 agents in the containment and/or treatment of solid tumour disease. Particularly, the compounds of the present invention are expected to be useful in the prevention or treatment of those tumours which are sensitive to inhibition of one or more of the multiple non-receptor tyrosine kinases such as c-Src kinase that are involved in the signal transduction steps which lead to the invasiveness and migratory ability of metastasising tumour cells. Further, the
25 compounds of the present invention are expected to be useful in the prevention or treatment of those tumours which are mediated alone or in part by inhibition of the enzyme c-Src, *i.e.* the compounds may be used to produce a c-Src enzyme inhibitory effect in a warm-blooded animal in need of such treatment. Specifically, the compounds of the present invention are expected to be useful in the prevention or treatment of solid tumour disease.

30 Thus according to this aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as

- 39 -

defined hereinbefore in the manufacture of a medicament for use as an anti-invasive agent in the containment and/or treatment of solid tumour disease.

According to a further feature of this aspect of the invention there is provided a method for producing an anti-invasive effect by the containment and/or treatment of solid
5 tumour disease in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as
10 defined hereinbefore in the manufacture of a medicament for use in the prevention or treatment of solid tumour disease in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a method for the prevention or treatment of solid tumour disease in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an
15 effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the prevention or
20 treatment of those tumours which are sensitive to inhibition of non-receptor tyrosine kinases such as c-Src kinase that are involved in the signal transduction steps which lead to the invasiveness and migratory ability of metastasising tumour cells.

According to a further feature of this aspect of the invention there is provided a method for the prevention or treatment of those tumours which are sensitive to inhibition of
25 non-receptor tyrosine kinases such as c-Src kinase that are involved in the signal transduction steps which lead to the invasiveness and migratory ability of metastasising tumour cells which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided the use of a
30 quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in providing a c-Src kinase inhibitory effect.

- 40 -

According to a further feature of this aspect of the invention there is provided a method for providing a c-Src kinase inhibitory effect which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

- 5 The anti-invasive treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to the quinazoline derivative of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents :-
- (i) other anti-invasion agents (for example metalloproteinase inhibitors like marimastat
10 and inhibitors of urokinase plasminogen activator receptor function);
- (ii) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimetabolites (for
15 example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside and hydroxyurea, or, for example, one of the preferred antimetabolites disclosed in European Patent Application No. 562734 such as
(2S)-2-{o-fluoro-p-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-yl)methyl]-
N-(prop-2-ynyl)amino]benzamido}-4-(tetrazol-5-yl)butyric acid); antitumour antibiotics (for
20 example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);
- (iii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene,
25 raloxifene, droloxifene and idoxifene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of
5 α -reductase such as finasteride;
- (iv) inhibitors of growth factor function, for example such inhibitors include growth factor
30 antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example

the EGFR tyrosine kinase inhibitors N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (ZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (CP 358774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), for example

5 inhibitors of the platelet-derived growth factor family and for example inhibitors of the hepatocyte growth factor family; and

(v) antiangiogenic agents such as those which inhibit vascular endothelial growth factor such as the compounds disclosed in International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354 and those that work by other mechanisms

10 (for example linomide, inhibitors of integrin $\alpha v \beta 3$ function and angiostatin).

Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products employ the compounds of this invention within the dosage range described hereinbefore and the other pharmaceutically-active agent within its approved dosage range.

15 According to this aspect of the invention there is provided a pharmaceutical product comprising a quinazoline derivative of the formula I as defined hereinbefore and an additional anti-tumour agent as defined hereinbefore for the conjoint treatment of cancer.

Although the compounds of the Formula I are primarily of value as therapeutic agents for use in warm-blooded animals (including man), they are also useful whenever it is required

20 to inhibit the effects of c-Src. Thus, they are useful as pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents.

The invention will now be illustrated in the following Examples in which, generally :

- (i) operations were carried out at ambient temperature, *i.e.* in the range 17 to 25°C and under an atmosphere of an inert gas such as argon unless otherwise stated;
- 25 (ii) evaporations were carried out by rotary evaporation *in vacuo* and work-up procedures were carried out after removal of residual solids by filtration;
- (iii) column chromatography (by the flash procedure) and medium pressure liquid chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385) or Merck Lichroprep RP-18 (Art. 9303) reversed-phase silica obtained from E. Merck, Darmstadt,
- 30 Germany or high pressure liquid chromatography (HPLC) was performed on C18 reverse phase silica, for example on a Dynamax C-18 60Å preparative reversed-phase column;
- (iv) yields, where present, are not necessarily the maximum attainable;

- 42 -

(v) in general, the end-products of the Formula I have satisfactory microanalyses and their structures were confirmed by nuclear magnetic resonance (NMR) and/or mass spectral techniques; fast-atom bombardment (FAB) mass spectral data were obtained using a Platform spectrometer and, where appropriate, either positive ion data or negative ion data were
5 collected; NMR chemical shift values were measured on the delta scale [proton magnetic resonance spectra were determined using a Jeol JNM EX 400 spectrometer operating at a field strength of 400MHz, Varian Gemini 2000 spectrometer operating at a field strength of 300MHz or a Bruker AM300 spectrometer operating at a field strength of 300MHz]; the following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m,
10 multiplet; br, broad;

(vi) intermediates were not generally fully characterised and purity was assessed by thin layer chromatographic, HPLC, infra-red (IR) and/or NMR analysis;

(vii) melting points are uncorrected and were determined using a Mettler SP62 automatic melting point apparatus or an oil-bath apparatus; melting points for the
15 end-products of the Formula I were determined after crystallisation from a conventional organic solvent such as ethanol, methanol, acetone, ether or hexane, alone or in admixture;

(viii) the following abbreviations have been used:-

DMF	<u>N,N</u> -dimethylformamide
DMSO	dimethylsulphoxide
THF	tetrahydrofuran

20

Example 1**4-(7-benzofuranylamino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline**

A mixture of 4-chloro-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline (0.1 g), 7-aminobenzofuran (0.057 g), isopropanol (4 ml) and a solution of hydrogen chloride in isopropanol (6M, 0.06 ml) was stirred and heated to 85°C for 3 hours. The resultant mixture was cooled to ambient temperature and the precipitate was isolated by filtration, washed in turn with a 1:1 mixture of diethyl ether and isopropanol and with diethyl ether and dried under vacuum. There was thus obtained the title compound (0.09 g) as a dihydrochloride salt; NMR Spectrum: (DMSO_d₆ and CF₃COOD) 2.35 (m, 2H), 2.9 (s, 3H), 3.45 (br m, 5H), 3.8 (br m, 5H), 4.05 (s, 3H), 4.35 (t, 2H), 7.1 (d, 1H), 7.45 (m, 3H), 7.75 (d, 1H), 8.05 (s, 1H), 8.25 (s, 1H), 8.8 (s, 1H); Mass Spectrum: M+H⁺ 448.

The 7-aminobenzofuran used as a starting material was prepared as follows :-

Hydrazine hydrate (0.45 ml) was added dropwise to a stirred mixture of 7-nitrobenzofuran (J. Med. Chem., 1988, 31, 1934; 0.5 g), Raney nickel (0.02 g) and methanol (9 ml) that had been warmed to 55°C. The resultant mixture was heated to reflux for 30 minutes. The catalyst was removed by filtration and the filtrate was evaporated. The residue was partitioned between methylene chloride and water. The organic phase was dried over magnesium sulphate and evaporated to give 7-aminobenzofuran (0.4 g) as an oil; NMR Spectrum: (DMSO_d₆) 5.25 (br s, 2H), 6.55 (d, 1H), 6.8 (m, 2H), 6.9 (t, 1H), 7.85 (d, 1H).

The 4-chloro-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline used as a starting material was prepared as follows :-

3-(4-Methylpiperazin-1-yl)propyl 4-toluenesulphonate was prepared as follows :-

A mixture of 3-bromopropanol (20 ml), N-methylpiperazine (29 ml), potassium carbonate (83 g) and ethanol (200 ml) was stirred and heated to reflux for 20 hours. The mixture was cooled to ambient temperature and filtered. The filtrate was evaporated and the residue was triturated under diethyl ether. The resultant mixture was filtered and the filtrate was evaporated. The residue was purified by distillation at about 60-70°C under about 0.2 mm Hg to give 1-(3-hydroxypropyl)-4-methylpiperazine (17 g); NMR Spectrum: (CDCl₃) 1.72 (m, 2H), 2.3 (s, 3H), 2.2-2.8 (m, 8H), 2.6 (t, 2H), 3.8 (t, 2H), 5.3 (br s, 1H).

4-Toluenesulphonyl chloride (3.2 g) was added to a stirred mixture of 1-(3-hydroxypropyl)-4-methylpiperazine (2.4 g), triethylamine (4.6 ml) and methylene chloride (60 ml) and the resultant mixture was stirred at ambient temperature for 2 hours. The

- 44 -

solution was washed in turn with a saturated aqueous sodium bicarbonate solution and with water and filtered through phase separating paper. The organic filtrate was evaporated to give 3-(4-methylpiperazin-1-yl)propyl 4-toluenesulphonate as an oil which crystallised on standing (3.7 g); Mass Spectrum: $M+H^+$ 313.

- 5 The trifluoroacetic acid salt of 4-(4-chloro-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline was prepared as follows :-

A mixture of 2-amino-4-benzyloxy-5-methoxybenzamide (J. Med. Chem., 1977, 20, 146-149; 10 g), (3-dimethylamino-2-azaprop-2-en-1-ylidene)dimethylammonium chloride (Gold's reagent, 7.4 g) and dioxane (100 ml) was stirred and heated to reflux for 24 hours.

- 10 Sodium acetate (3.02 g) and acetic acid (1.65 ml) were added and the reaction mixture was heated for a further 3 hours. The mixture was evaporated and water was added to the residue. The resultant solid was collected by filtration, washed with water and dried. The material was recrystallised from acetic acid to give 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (8.7 g).

- 15 After repetition of the reaction so described, a mixture of 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (20.3 g), thionyl chloride (440 ml) and DMF (1.75 ml) was heated to reflux for 4 hours. The thionyl chloride was evaporated under vacuum and the residue was azeotroped with toluene three times to give 7-benzyloxy-4-chloro-6-methoxyquinazoline.

- 20 A mixture of the 7-benzyloxy-4-chloro-6-methoxyquinazoline so obtained, potassium carbonate (50 g) and 4-chloro-2-fluorophenol (8.8 ml) and DMF (500 ml) was stirred and heated to 100°C for 5 hours. The mixture was allowed to cool to ambient temperature, poured into water (2 L) and stirred at ambient temperature for a few minutes. The resultant solid was isolated and washed with water. The solid was dissolved in methylene chloride and the
- 25 solution was filtered and treated with decolourising charcoal. The resultant solution was filtered and evaporated to give a solid which was triturated under diethyl ether. There was thus obtained 7-benzyloxy-4-(4-chloro-2-fluorophenoxy)-6-methoxyquinazoline (23.2 g); NMR Spectrum: ($DMSO-d_6$) 3.98 (s, 3H), 5.34 (s, 2H), 7.42 (m, 9H), 7.69 (m, 1H), 8.55 (s, 1H).

- 30 A mixture of the material so obtained and trifluoroacetic acid (15 ml) was heated to reflux for 3 hours. The reaction mixture was allowed to cool, toluene was added and the mixture was evaporated. The residue was triturated under diethyl ether and then under

- 45 -

acetone. The resultant precipitate was isolated and dried to give 4-(4-chloro-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline trifluoroacetate salt (21.8 g) which was used without further purification.

Thereafter, a mixture of the trifluoroacetic acid salt of 4-(4-chloro-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline (3.2 g), 3-(4-methylpiperazin-1-yl)propyl 4-toluenesulphonate (3.0 g), potassium carbonate (6.1 g) and DMF (60 ml) was stirred at 90°C for 5 hours. The resultant mixture was cooled to ambient temperature, poured into water (700 ml) and extracted with ethyl acetate (5 times). The combined extracts were washed in turn with water, a saturated aqueous sodium bicarbonate solution, water and brine. The ethyl acetate solution was dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 100: 8:1 mixture of methylene chloride, methanol and a concentrated aqueous ammonium hydroxide solution (0.880 g/ml) as eluent. The material so obtained was triturated under diethyl ether. There was thus obtained 4-(4-chloro-2-fluorophenoxy)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline (1.64 g); NMR Spectrum: (DMSO-d₆) 1.95 (m, 2H), 2.14 (s, 3H), 2.35 (m, 8H), 2.44 (t, 2H), 3.96 (s, 3H), 4.22 (t, 2H), 7.38 (s, 1H), 7.4 (m, 1H), 7.54 (m, 2H), 7.68 (m, 1H), 8.55 (s, 1H).

After repetition of the previous reaction, a mixture of 4-(4-chloro-2-fluorophenoxy)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline (2.6 g) and 2N aqueous hydrochloric acid solution (45 ml) was stirred and heated to 95°C for 2 hours. The mixture was cooled to ambient temperature and basified by the addition of solid sodium bicarbonate. The mixture was evaporated and the residue was purified by column chromatography on silica using a 50: 8:1 mixture of methylene chloride, methanol and a concentrated aqueous ammonium hydroxide solution (0.880 g/ml) as eluent. There was thus obtained 6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]-3,4-dihydroquinazolin-4-one (1.8 g.); Mass Spectrum: M+H⁺ 333.

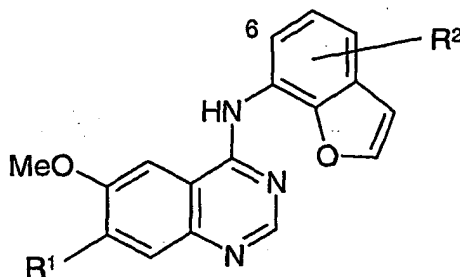
After repetition of the previous reaction, a mixture of 6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]-3,4-dihydroquinazolin-4-one (2.15 g), thionyl chloride (25 ml) and DMF (0.18 ml) was stirred and heated to reflux for 2 hours. The thionyl chloride was evaporated under vacuum and the residue azeotroped twice with toluene. The residue was taken up in water, basified by the addition of a saturated aqueous sodium bicarbonate solution and extracted with methylene chloride (4 times). The combined extracts were washed in turn with water and brine and filtered through phase separating paper. The filtrate

- 46 -

was evaporated under vacuum and the residue was purified by column chromatography on silica using a 100: 8:1 mixture of methylene chloride, methanol and a concentrated aqueous ammonium hydroxide solution (0.880 g/ml) as eluent. The solid so obtained was triturated under acetone, filtered and dried to give 4-chloro-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline (1.2 g); Mass Spectrum: $M+H^+$ 351.

Example 2

Using an analogous procedure to that described in Example 1, the appropriate 4-chloroquinazoline was reacted with the appropriate 7-aminobenzofuran to give the compounds described in Table I. Unless otherwise stated, each compound described in Table I was obtained as a dihydrochloride salt.

Table I

No.	R ¹	R ²	Note
1	3-morpholinopropoxy	hydrogen	[1]
2	3-morpholinopropoxy	5-methoxy	[2]
3	3-(4-methylpiperazin-1-yl)propoxy	5-methoxy	[3]
4	3-morpholinopropoxy	3-chloro	[4]
5	3-(4-methylpiperazin-1-yl)propoxy	3-chloro	[5]
6	3-morpholinopropoxy	5-fluoro	[6]
7	3-(4-methylpiperazin-1-yl)propoxy	5-fluoro	[7]
8	2-acetoxy-3-morpholinopropoxy	3-chloro	[8]
9	2-acetoxy-3-(N-isopropyl-N-methylamino)propoxy	3-chloro	[9]
10	2-acetoxy-3-(4-cyanomethylpiperazin-1-yl)propoxy	3-chloro	[10]
11	2-acetoxy-3-pyrrolidin-1-ylpropoxy	3-chloro	[11]
12	2-acetoxy-3-piperidinopropoxy	3-chloro	[12]

- 47 -

Notes

- [1] The product gave the following characterising data; NMR Spectrum: (DMSO-d₆ and CF₃COOD) 2.35 (m, 2H), 3.15 (t, 2H), 3.35 (t, 2H), 3.55 (d, 2H), 3.75 (t, 2H), 4.05 (t, 3H), 4.1 (m, 2H), 4.35 (t, 2H), 7.1 (d, 1H), 7.45 (m, 3H), 7.75 (d, 1H), 8.05 (d, 1H), 8.25 (s, 1H),
5 8.85 (s, 1H); Mass Spectrum: M+H⁺ 435.

The 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline used as a starting material was prepared as follows :-

- A mixture of 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (35 g), thionyl chloride (440 ml) and DMF (1.75 ml) was heated to reflux for 4 hours. The thionyl chloride
10 was evaporated under vacuum and the residue was azeotroped with toluene three times. The residue was dissolved in N-methylpyrrolidin-2-one (250 ml) to give a solution of 7-benzyloxy-4-chloro-6-methoxyquinazoline.

- Phenol (29.05 g) was dissolved in N-methylpyrrolidin-2-one (210 ml) and sodium hydride (60% dispersion in mineral oil; 11.025 g) was added in portions with cooling. The
15 resultant mixture was stirred at ambient temperature for 3 hours. The resultant viscous suspension was diluted with N-methylpyrrolidin-2-one (180 ml) and stirred overnight. The above-mentioned solution of 7-benzyloxy-4-chloro-6-methoxyquinazoline was added and the resultant suspension was stirred and heated to 100°C for 2.5 hours. The mixture was allowed to cool to ambient temperature and poured into water (1.5 L) with vigorous stirring. The
20 precipitate was collected by filtration, washed with water and dried under vacuum. The material so obtained was dissolved in methylene chloride and the solution was washed with brine and filtered through phase separating paper. The solution was evaporated under vacuum and the resultant residue was triturated under diethyl ether. There was thus obtained 7-benzyloxy-6-methoxy-4-phenoxyquinazoline (87.8 g); NMR Spectrum: (CDCl₃) 4.09 (s,
25 3H), 5.34 (s, 2H), 7.42 (m, 12H), 7.63 (s, 1H).

- A mixture of a portion (36.95 g) of the material so obtained and trifluoroacetic acid (420 ml) was heated to reflux for 3 hours. The reaction mixture was allowed to cool and evaporated under vacuum. The residue was stirred mechanically under water, basified by the addition of a saturated aqueous sodium bicarbonate solution and stirred overnight. The water
30 was decanted and the residual solid was suspended in acetone. After stirring, the white solid was collected by filtration, washed with acetone and dried to give 7-hydroxy-6-methoxy-

- 48 -

4-phenoxyquinazoline (26.61 g); NMR Spectrum: (DMSO_d₆) 3.97 (s, 3H), 7.22 (s, 1H), 7.3 (m, 3H), 7.47 (t, 2H), 7.56 (s, 1H), 8.47 (s, 1H), 10.7 (s, 1H).

A mixture of 7-hydroxy-6-methoxy-4-phenoxyquinazoline (25.27 g), 3-morpholinopropyl chloride (18.48 g), potassium carbonate (39.1 g) and DMF (750 ml) was stirred and heated to 90°C for 3 hours. The mixture was allowed to cool to ambient temperature and filtered. The filtrate was evaporated and the residue was triturated under ethyl acetate. There was thus obtained 6-methoxy-7-(3-morpholinopropoxy)-4-phenoxyquinazoline (31.4 g); NMR Spectrum: (DMSO_d₆) 1.97 (m, 2H), 2.39 (t, 4H), 2.47 (t, 2H), 3.58 (t, 4H), 3.95 (s, 3H), 4.23 (t, 2H), 7.31 (m, 3H), 7.36 (s, 1H), 7.49 (t, 2H), 7.55 (s, 1H), 8.52 (s, 1H).

A mixture of the material so obtained and 6N aqueous hydrochloric acid solution (800 ml) was stirred and heated to reflux for 1.5 hours. The reaction mixture was decanted and concentrated to a volume of 250 ml. The mixture was basified to pH9 by the addition of a saturated aqueous sodium bicarbonate solution and extracted with methylene chloride (4x400 ml). The combined extracts were filtered through phase separating paper and the filtrate was evaporated. The resultant solid was triturated under ethyl acetate to give 6-methoxy-7-(3-morpholinopropoxy)-3,4-dihydroquinazolin-4-one (23.9 g); NMR Spectrum: (DMSO_d₆) 1.91 (m, 2H), 2.34 (t, 4H), 2.42 (t, 2H), 3.56 (t, 4H), 3.85 (s, 3H), 4.12 (t, 2H), 7.11 (s, 1H), 7.42 (s, 1H), 7.96 (s, 1H), 12.01 (s, 1H).

A mixture of the material so obtained, thionyl chloride (210 ml) and DMF (1.8 ml) was heated to reflux for 1.5 hours. The thionyl chloride was removed by evaporation under vacuum and the residue was azeotroped with toluene three times. The residue was taken up in water and basified to pH8 by the addition of a saturated aqueous sodium bicarbonate solution. The resultant aqueous layer was extracted with methylene chloride (4x400 ml). The combined extracts were washed with water and with brine and dried over magnesium sulphate. The solution was filtered and evaporated. The resultant solid was triturated under ethyl acetate to give 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (17.39 g); NMR Spectrum: (CDCl₃) 2.1-2.16 (m, 2H), 2.48 (br s, 4H), 2.57 (t, 2H), 3.73 (t, 4H), 4.05 (s, 3H), 4.29 (t, 2H), 7.36 (s, 1H), 7.39 (s, 1H), 8.86 (s, 1H).

The 3-morpholinopropyl chloride used as a reagent was obtained as follows:-

A mixture of morpholine (52.2 ml), 1-bromo-3-chloropropane (30 ml) and toluene (180 ml) was heated to 70°C for 3 hours. The solid was removed by filtration and the filtrate

was evaporated under vacuum. The resultant oil was decanted from the additional solid which was deposited and the oil was purified by vacuum distillation to yield 3-morpholinopropyl chloride (37.91 g); NMR Spectrum: (DMSO_d₆) 1.85 (m, 2H), 2.3 (t, 4H), 2.38 (t, 2H), 3.53 (t, 4H), 3.65 (t, 2H).

- 5 [2] Pentan-2-ol was used in place of isopropanol as the reaction solvent and the reaction mixture was heated to 85°C for 1 hour. The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃COOD) 2.35 (m, 2H), 3.15 (m, 2H), 3.35 (t, 2H), 3.55 (d, 2H), 3.75 (t, 2H), 3.85 (s, 3H), 4.0 (s, 3H), 4.05 (m, 2H), 4.35 (t, 2H), 7.0 (d, 1H), 7.1 (d, 1H), 7.25 (d, 1H), 7.4 (s, 1H), 8.0 (d, 1H), 8.2 (s, 1H), 8.85 (s, 1H); Mass Spectrum: M+H⁺ 465.

- 10 The 7-amino-5-methoxybenzofuran used as a starting material was prepared as follows :-

2-Hydroxy-5-methoxybenzaldehyde was reacted with ceric ammonium nitrate according to the procedure described in Synth. Comm., 1999, 1201 to give 2-hydroxy-5-methoxy-3-nitro-benzaldehyde.

- 15 A mixture of 2-hydroxy-5-methoxy-3-nitrobenzaldehyde (1 g), diethyl bromomalonate (0.95 ml), potassium carbonate (1.05 g), tetrabutylammonium bromide (0.163 g) and toluene (20 ml) was stirred and heated to reflux in a Dean & Stark apparatus for 20 hours. The mixture was cooled to ambient temperature, filtered and the filtrate was evaporated. The residue was dissolved in methylene chloride and the solution was washed in turn with water, 20 with a 1N aqueous potassium hydroxide solution and with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 4:1 mixture of methylene chloride and petroleum ether (b.p. 60-80°C) as eluent. There was thus obtained ethyl 5-methoxy-7-nitrobenzofuran-2-carboxylate (0.264 g); NMR Spectrum: (DMSO_d₆) 1.35 (t, 3H), 3.9 (s, 3H), 4.4 (q, 2H), 7.8 (d, 1H), 7.85 (s, 1H), 7.9 (d, 1H).

- 25 After repetition of the preceding reaction, a mixture of ethyl 5-methoxy-7-nitrobenzofuran-2-carboxylate (0.5 g), 2N aqueous potassium hydroxide solution (1.8 ml) and ethanol (20 ml) was stirred and heated to reflux for 1 hour. The ethanol was evaporated and the residue was dissolved in water. The solution was acidified to pH1 by the addition of 6N aqueous hydrochloric acid. The resultant precipitate was isolated, washed with water and 30 dried under vacuum over phosphorus pentoxide to give 5-methoxy-7-nitrobenzofuran-2-carboxylic acid (0.33 g); NMR Spectrum: (DMSO_d₆) 3.95 (s, 3H), 7.8 (s, 1H), 7.85 (d, 1H), 7.9 (d, 1H).

- 50 -

A mixture of the material so obtained, cupric (II) oxide (0.016 g), copper powder (0.015 g) and quinoline (3 ml) was heated to 220°C for 30 minutes. The mixture was cooled to ambient temperature and filtered. The filtrate was partitioned between diethyl ether and 2N aqueous hydrochloric acid. The organic phase was dried over magnesium sulphate and
5 evaporated. The residue was purified by column chromatography on silica using a 3:2 mixture of petroleum ether (b.p. 60-80°C) and ethyl acetate as eluent. There was thus obtained 5-methoxy-7-nitrobenzofuran (0.25 g); NMR Spectrum: (DMSO_d₆), 3.9 (s, 3H), 7.15 (d, 1H), 7.7 (d, 1H), 7.75 (d, 1H), 8.25 (d, 1H).

Hydrazine hydrate (0.188 ml) was added dropwise to a stirred mixture of 5-methoxy-
10 7-nitrobenzofuran (0.25 g), Raney nickel (0.02 g) and methanol (10 ml) that had been warmed to 55-60°C. The reaction mixture was then heated to reflux for 45 minutes. The catalyst was removed by filtration and the filtrate was evaporated. The residue was partitioned between methylene chloride and water. The organic phase was dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 3:2 mixture
15 of petroleum ether (b.p. 60-80°C) and ethyl acetate as eluent. There was thus obtained 7-amino-5-methoxybenzofuran (0.153 g); NMR Spectrum: (DMSO_d₆) 3.7 (s, 3H), 5.3 (s, 2H), 6.2 (d, 1H), 6.35 (d, 1H), 6.75 (d, 1H), 7.85 (d, 1H).

[3] Pentan-2-ol was used in place of isopropanol as the reaction solvent and the reaction mixture was heated to 120°C for 4 hours. The product gave the following characterising data;
20 NMR Spectrum: (DMSO_d₆ and CF₃COOD) 2.35 (m, 2H), 2.95 (s, 3H), 3.4 (br s, 5H), 3.8 (br s, 5H), 3.85 (s, 3H), 4.05 (s, 3H), 4.35 (t, 2H), 7.0 (d, 1H), 7.10 (d, 1H), 7.25 (d, 1H), 7.4 (s, 1H), 8.0 (d, 1H), 8.25 (s, 1H), 8.85 (s, 1H); Mass Spectrum: M+H⁺ 478.

[4] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃COOD) 2.3 (m, 2H), 3.15 (t, 2H), 3.35 (t, 2H), 3.55 (d, 2H), 3.75 (t, 2H), 4.0 (s, 3H), 4.05
25 (m, 2H), 4.35 (t, 2H), 7.3 (s, 1H), 7.55 (t, 1H), 7.6 (d, 1H), 7.7 (d, 1H), 8.2 (s, 1H), 8.4 (s, 1H), 8.85 (s, 1H); Mass Spectrum: M+H⁺ 469.

The 7-amino-3-chlorobenzofuran used as a starting material was prepared as follows :-

7-Nitrobenzofuran (1.2 g) was dissolved in glacial acetic acid (12 ml) and chlorine gas was bubbled through the solution for 30 minutes whilst the temperature of the reaction
30 mixture was maintained at about 18°C. The reaction mixture was evaporated and the residue was purified by column chromatography using a 1:1 mixture of petroleum ether (b.p. 60-80°C) and ethyl acetate as eluent. There was thus obtained a mixture of the *cis*- and

- 51 -

trans- isomers of 2,3-dichloro-7-nitro-2,3-dihydrobenzofuran (0.77 g); Mass Spectrum: $M+H^+$ 233.

After repetition of the preceding reaction, *cis*- and *trans*- 2,3-dichloro-7-nitro-2,3-dihydrobenzofuran (0.85 g) was dissolved in ethanol (35 ml) and a 0.8N aqueous potassium hydroxide solution (45.5 ml) was added. The reaction mixture was stirred at ambient temperature for 1.25 hours. The mixture was concentrated by evaporation, water was added and the mixture was acidified to pH2 by the addition of 6N aqueous hydrochloric acid. The mixture was extracted with diethyl ether. The organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated. There was thus obtained 3-chloro-7-nitrobenzofuran (0.7 g) as a colorless solid; NMR Spectrum: (DMSO_d₆) 7.65 (t, 1H), 8.15 (d, 1H), 8.3 (d, 1H), 8.65 (s, 1H).

The material so obtained was dissolved in methanol (25 ml) was the solution was added dropwise during 5 minutes to a stirred mixture of hydrazine hydrate (0.81 ml), Raney nickel (0.16 g) and methanol (30 ml) which had been heated to 60°C. The resultant reaction mixture was then heated to reflux for 5 minutes. The reaction mixture was cooled to ambient temperature and the catalyst was removed by filtration. The filtrate was evaporated and the residue was partitioned between methylene chloride and water. The organic phase was dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 1:1 mixture of petroleum ether (b.p. 60-80°C) and ethyl acetate as eluent. There was thus obtained 7-amino-3-chlorobenzofuran (0.41 g); NMR Spectrum: (DMSO_d₆) 5.5 (br s, 2H), 6.65 (d, 1H), 6.75 (d, 1H), 7.05 (t, 1H), 8.2 (s, 1H).

[5] Pentan-2-ol was used in place of isopropanol as the reaction solvent and the reaction mixture was heated to 110°C for 5 hours. The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃COOD) 2.35 (m, 2H), 2.95 (s, 3H), 3.4 (br s, 5H), 3.8 (br s, 5H), 4.05 (s, 3H), 4.35 (m, 2H), 7.4 (s, 1H), 7.55 (t, 1H), 7.6 (d, 1H), 7.7 (d, 1H), 8.25 (s, 1H), 8.4 (s, 1H), 8.85 (s, 1H); Mass Spectrum: $M+H^+$ 482.

[6] Pentan-2-ol was used in place of isopropanol as the reaction solvent and the reaction mixture was heated to 85°C for 1 hour. The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃COOD) 2.35 (m, 2H), 3.15 (m, 2H), 3.35 (t, 2H), 3.55 (d, 2H), 3.75 (t, 2H), 4.0 (m, 2H), 4.05 (s, 3H), 4.35 (t, 2H), 7.1 (d, 1H), 7.4 (m, 2H), 7.6 (m, 1H), 8.1 (d, 1H), 8.25 (s, 1H), 8.9 (s, 1H); Mass Spectrum: $M+H^+$ 453.

The 7-amino-5-fluorobenzofuran used as a starting material was prepared as follows :-

- 52 -

Allyl bromide (6 ml) was added to a stirred mixture of 3-fluoro-2-nitrophenol (10 g), 1,5,7-triazabicyclo[4,4,0]dec-5-ene (11.5 g) and DMF (120 ml) and the reaction mixture was stirred at ambient temperature for 20 hours. The reaction mixture was then heated to 50°C for 1.5 hours. The mixture was evaporated and the residue was partitioned between diethyl ether and water. The organic phase was washed in turn with a 1N aqueous hydrochloric acid solution, water and brine, dried over magnesium sulphate and evaporated. There was thus obtained 4-allyloxy-3-nitro-1-fluorobenzene (9.6 g); NMR Spectrum: (DMSO_d₆) 4.85 (d, 2H), 5.3 (d, 1H), 5.45 (d, 1H), 6.05 (m, 1H), 7.4 (m, 1H), 7.6 (m, 1H), 7.9 (m, 1H).

A mixture of 4-allyloxy-3-nitro-1-fluorobenzene (8 g) and 1,2-dichlorobenzene (14 ml) was heated to 230°C for 32 minutes in a microwave oven (651W for 3 minutes to raise the temperature to 230°C and then 300W for 29 min). The solvent was evaporated and the residue was mixed with methylene chloride (30 ml) and filtered. The filtrate was evaporated and the residue was purified by column chromatography on silica using a 4:1 mixture of petroleum ether (b.p. 60-80°C) and methylene chloride as eluent. There was thus obtained 2-allyl-4-fluoro-6-nitrophenol (3.5 g) as an oil; NMR Spectrum: (DMSO_d₆) 3.45 (d, 2H), 5.1 (d, 2H), 6.0 (m, 1H), 7.5 (m, 1H), 7.75 (m, 1H), 10.4 (br s, 1H).

The material so obtained was dissolved in methanol and cooled to -78°C. Ozone was bubbled through the solution for 30 minutes. Dimethyl sulfide (5.4 ml) was added and the reaction mixture was allowed to warm to ambient temperature. The mixture was evaporated and the residue was partitioned between diethyl ether and water. The organic phase was washed in turn with water and brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 1:1 mixture of petroleum ether (b.p. 60-80°C) and methylene chloride and then a 9:1 mixture of methylene chloride and diethyl ether as eluent. There was thus obtained 2-(5-fluoro-2-hydroxy-3-nitrophenyl)acetaldehyde which was immediately suspended in 85% phosphoric acid (18 ml) and the mixture was heated to 100°C for 1 hour. The mixture was cooled to ambient temperature and partitioned between diethyl ether and water. The organic phase was washed in turn with water and brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 1:1 mixture of petroleum ether (b.p. 60-80°C) and methylene chloride as eluent. There was thus obtained 5-fluoro-7-nitrobenzofuran (1.3 g); NMR Spectrum: (DMSO_d₆) 7.2 (d, 1H), 8.05 (m, 2H), 8.35 (d, 1H).

- 53 -

Hydrazine hydrate (0.522 ml) was added dropwise to a stirred mixture of 5-fluoro-7-nitrobenzofuran (0.65 g), Raney nickel (0.03 g) and methanol (12 ml) that had been warmed to 55-60°C. The reaction mixture was then heated to reflux for 45 minutes. The catalyst was removed by filtration and the filtrate was evaporated. The residue was partitioned between methylene chloride and water. The organic phase was dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of petroleum ether (b.p. 60-80°C) and methylene chloride as eluent. There was thus obtained 7-amino-5-fluorobenzofuran (0.206 g); NMR Spectrum: (DMSO_d₆) 5.65 (br s, 2H), 6.3 (m, 1H), 6.55 (m, 1H), 6.8 (d, 1H), 7.9 (d, 1H).

10 [7] Pentan-2-ol was used in place of isopropanol as the reaction solvent and the reaction mixture was heated to 115°C for 5 hours. The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃COOD) 2.35 (m, 2H), 2.9 (s, 3H), 3.4 (br s, 5H), 3.8 (br s, 5H), 4.05 (s, 3H), 4.35 (t, 2H), 7.1 (d, 1H), 7.4 (m, 2H), 7.55 (m, 1H), 8.1 (d, 1H), 8.3 (s, 1H), 8.85 (s, 1H); Mass Spectrum: M+H⁺ 466.

15 [8] The product gave the following characterising data; Mass Spectrum: M+H⁺ 527 and 529.

The 7-(2-acetoxy-3-morpholinopropoxy)-4-chloro-6-methoxyquinazoline used as a starting material was prepared as follows :-

Sodium hydride (60% suspension in mineral oil, 1.44 g) was added portionwise during 20 20 minutes to a solution of 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (International Patent Application WO 97/22596, Example 1 thereof; 8.46 g) in DMF (70 ml). The mixture was stirred at ambient temperature for 1.5 hours. Chloromethyl pivalate (5.65 g) was added dropwise and the mixture was stirred at ambient temperature for 2 hours. The mixture was diluted with ethyl acetate (100 ml) and poured onto a mixture (400 ml) of ice and 25 water containing 2N aqueous hydrochloric acid (4 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined extracts were washed with brine, dried over magnesium sulphate and evaporated. The residue was triturated under a mixture of diethyl ether and petroleum ether (b.p. 60-80°C) and the resultant solid was collected and dried under vacuum. There was thus obtained 7-benzyloxy-6-methoxy-30 3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (10 g); NMR Spectrum: (DMSO_d₆) 1.11 (s, 9H), 3.89 (s, 3H), 5.3 (s, 2H), 5.9 (s, 2H), 7.27 (s, 1H), 7.35 (m, 1H), 7.47 (t, 2H), 7.49 (d, 2H), 7.51 (s, 1H), 8.34 (s, 1H).

- 54 -

A mixture of a portion (7 g) of the material so obtained, 10% palladium-on-charcoal catalyst (0.7 g), DMF (50 ml), methanol (50 ml), acetic acid (0.7 ml) and ethyl acetate (250 ml) was stirred under an atmosphere pressure of hydrogen for 40 minutes. The catalyst was removed by filtration and the solvent was evaporated. The residue was triturated under diethyl ether and the resultant solid was collected and dried under vacuum. There was thus obtained 7-hydroxy-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (4.36 g); NMR Spectrum: (DMSO_d₆) 1.1 (s, 9H), 3.89 (s, 3H), 5.89 (s, 2H), 7.0 (s, 1H), 7.48 (s, 1H), 8.5 (s, 1H).

A mixture of 7-hydroxy-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (40 g), 2,3-epoxypropyl bromide (16.8 ml), potassium carbonate (36 g) and DMF (400 ml) was stirred and heated to 70°C for 1.5 hours. The mixture was poured into an ice-water mixture (1.5 L) and the resultant precipitate was isolated, washed in turn with water and diethyl ether and dried under vacuum over phosphorus pentoxide. There was thus obtained 7-(2,3-epoxypropoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (46.7 g).

A mixture of a portion (8 g) of the material so obtained, morpholine (5.8 ml) and chloroform (120 ml) was heated to reflux for 16 hours. The mixture was evaporated and the residue was purified by column chromatography on silica using a 19:1 mixture of methylene chloride and methanol as eluent. There was thus obtained 7-(2-hydroxy-3-morpholinopropoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one as a foam (8.2 g); NMR Spectrum: (CDCl₃) 1.2 (s, 9H), 2.5 (m, 2H), 2.6 (m, 2H), 2.7 (m, 2H), 3.5 (br s, 1H), 3.75 (m, 4H), 3.95 (s, 3H), 4.15 (m, 2H), 4.25 (m, 1H), 5.95 (s, 2H), 7.15 (s, 1H), 7.65 (s, 1H), 8.2 (s, 1H).

A mixture of the material so obtained and a saturated methanolic ammonia solution was stirred at ambient temperature for 24 hours. The mixture was evaporated and the resultant solid was washed with diethyl ether and a 19:1 mixture of diethyl ether and methylene chloride. There was thus obtained 7-(2-hydroxy-3-morpholinopropoxy)-6-methoxy-3,4-dihydroquinazolin-4-one (6.34 g); NMR Spectrum: (DMSO_d₆) 2.4 (m, 6H), 3.55 (m, 4H), 3.85 (s, 3H), 4.0 (m, 2H), 4.15 (m, 1H), 4.95 (br s, 1H), 7.15 (s, 1H), 7.45 (s, 1H), 7.95 (s, 1H).

A mixture of a portion (5.2 g) of the material so obtained, acetic anhydride (20 ml) and pyridine (1 ml) was stirred at ambient temperature for 30 minutes. The resultant mixture was poured into an ice-water mixture and stirred for 30 minutes. The mixture was then cooled in

- 55 -

an ice-bath and a saturated solution of sodium bicarbonate was slowly added to adjust the pH to 9. The mixture was extracted with methylene chloride and the organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 93:7 mixture of methylene chloride and methanol as eluent. There was thus obtained 7-(2-acetoxy-3-morpholinopropoxy)-6-methoxy-3,4-dihydroquinazolin-4-one as a solid (5 g); NMR Spectrum: (DMSO_d₆) 2.05 (s, 3H), 2.4 (m, 4H), 2.6 (m, 2H), 3.55 (m, 4H), 3.85 (s, 3H), 4.35 (m, 2H), 5.25 (m, 1H), 7.2 (s, 1H), 7.45 (s, 1H), 8.0 (s, 1H); Mass Spectrum: M+H⁺ 378.

A mixture of the material so obtained, thionyl chloride (60 ml) and DMF (0.5 ml) was heated to reflux for 1 hour. The mixture was evaporated, toluene was added and the mixture was evaporated. A mixture of ice and water was added to the residue and the mixture was basified to pH 8.5 by the addition of a saturated aqueous sodium bicarbonate solution. The mixture was extracted with methylene chloride. The organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 97:3 mixture of methylene chloride and methanol as eluent. There was thus obtained 7-(2-acetoxy-3-morpholinopropoxy)-4-chloro-6-methoxyquinazoline as a foam (4.56 g); NMR Spectrum: (CDCl₃) 2.1 (s, 3H), 2.55 (m, 4H), 2.7 (d, 2H), 3.7 (m, 4H), 4.05 (s, 3H), 4.35 (m, 1H), 4.45 (m, 1H), 5.45 (m, 1H), 7.4 (d, 2H), 8.85 (s, 1H); Mass Spectrum: M+H⁺ 396 and 398.

[9] The product gave the following characterising data; Mass Spectrum: M+H⁺ 513.

The 7-[2-acetoxy-3-(N-isopropyl-N-methylamino)propoxy]-4-chloro-6-methoxyquinazoline used as a starting material was prepared as follows :-

7-(2,3-Epoxypropoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one was reacted with N-isopropyl-N-methylamine using an analogous procedure to that described in the fourth paragraph of the portion of Note [8] immediately above that is concerned with the preparation of starting materials. There was thus obtained 7-[2-hydroxy-3-(N-isopropyl-N-methylamino)propoxy]-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one.

The material so obtained was taken through an analogous sequence of reactions to those described in the fifth to seventh paragraphs of the portion of Note [8] immediately above that is concerned with the preparation of starting materials. There was thus obtained

7-[2-acetoxy-3-(N-isopropyl-N-methylamino)propoxy]-4-chloro-6-methoxyquinazoline; NMR Spectrum: (CDCl₃) 1.0 (d, 6H), 2.1 (s, 3H), 2.3 (s, 3H), 2.6 (m, 1H), 2.75 (m, 1H), 2.85 (m,

- 56 -

1H), 4.05 (s, 3H), 4.35 (m, 1H), 4.45 (m, 1H), 5.35 (m, 1H), 7.25 (s, 1H), 7.4 (s, 1H), 8.85 (s, 1H).

[10] The product gave the following characterising data; Mass Spectrum: $M+H^+$ 565.

The 7-[2-acetoxy-3-(4-cyanomethylpiperazin-1-yl)propoxy]-4-chloro-

5 6-methoxyquinazoline used as a starting material was prepared as follows :-

7-(2,3-Epoxypropoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one was reacted with 1-cyanomethylpiperazine using an analogous procedure to that described in the fourth paragraph of the portion of Note [8] immediately above that is concerned with the preparation of starting materials. There was thus obtained 7-[3-(4-cyanomethylpiperazin-10 1-yl)-2-hydroxypropoxy]-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one.

The material so obtained was taken through an analogous sequence of reactions to those described in the fifth to seventh paragraphs of the portion of Note [8] immediately above that is concerned with the preparation of starting materials. There was thus obtained 7-[2-acetoxy-3-(4-cyanomethylpiperazin-1-yl)propoxy]-4-chloro-6-methoxyquinazoline;
15 NMR Spectrum: ($CDCl_3$) 2.1 (s, 3H), 2.65 (br s, 10H), 3.5 (s, 2H), 4.05 (s, 3H), 4.4 (m, 2H), 5.45 (m, 1H), 7.25 (s, 1H), 7.4 (s, 1H), 8.85 (s, 1H); Mass Spectrum: $M+H^+$ 434 and 436.

The 1-cyanomethylpiperazine used as a starting material was prepared as follows :-

A mixture of 1-(tert-butoxycarbonyl)piperazine (5 g), 2-chloroacetonitrile (1.9 ml), potassium carbonate (4 g) and DMF (20 ml) was stirred at ambient temperature for 16 hours.
20 A saturated aqueous ammonium chloride solution was added and the mixture was extracted with ethyl acetate. The organic phase was dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using diethyl ether as eluent. There was thus obtained 1-(tert-butoxycarbonyl)-4-cyanomethylpiperazine as a solid (5.7 g);
NMR Spectrum: ($CDCl_3$) 1.45 (s, 9H), 2.5 (m, 4H), 3.45 (m, 4H), 3.55 (s, 2H).

25 A mixture of the material so obtained, trifluoroacetic acid (20 ml) and methylene chloride (25 ml) was stirred at ambient temperature for 4 hours. The mixture was evaporated, toluene was added and the mixture was evaporated again. The residue was purified by column chromatography on silica using a 9:1 mixture of methylene chloride and methanol as eluent. There was thus obtained 1-cyanomethylpiperazine trifluoroacetate salt which was
30 treated with solid sodium bicarbonate in a mixture of methylene chloride, ethyl acetate and methanol to give the free base form (2.9 g); NMR Spectrum: ($CDCl_3$ and $DMSO-d_6$) 2.7 (m, 4H), 3.2 (m, 4H), 3.6 (s, 2H), 6.2 (br s, 1H).

- 57 -

[11] The product gave the following characterising data; Mass Spectrum $M+H^+$ 511.

The 7-(2-acetoxy-3-pyrrolidin-1-ylpropoxy)-4-chloro-6-methoxyquinazoline used as a starting material was prepared as follows :-

7-(2,3-Epoxypropoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one
5 was reacted with pyrrolidine using an analogous procedure to that described in the fourth paragraph of the portion of Note [8] immediately above that is concerned with the preparation of starting materials. There was thus obtained 7-(2-hydroxy-3-pyrrolidin-1-ylpropoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one.

The material so obtained was taken through an analogous sequence of reactions to
10 those described in the fifth to seventh paragraphs of the portion of Note [8] immediately above that is concerned with the preparation of starting materials. There was thus obtained 7-(2-acetoxy-3-pyrrolidin-1-ylpropoxy)-4-chloro-6-methoxyquinazoline; NMR Spectrum: ($CDCl_3$ and CD_3CO_2D) 2.05 (s, 4H), 2.15 (s, 3H), 3.45 (br s, 4H), 3.65 (m, 2H), 4.05 (s, 3H), 4.4 (d, 2H), 5.65 (m, 1H), 7.4 (s, 1H), 7.55 (s, 1H), 8.9 (s, 1H).

15 [12] The product gave the following characterising data; Mass Spectrum $M+H^+$ 525.

The 7-(2-acetoxy-3-piperidinopropoxy)-4-chloro-6-methoxyquinazoline used as a starting material was prepared as follows :-

7-(2,3-Epoxypropoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one
was reacted with piperidine using an analogous procedure to that described in the fourth
20 paragraph of the portion of Note [8] immediately above that is concerned with the preparation of starting materials. There was thus obtained 7-(2-hydroxy-3-piperidinopropoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one.

The material so obtained was taken through an analogous sequence of reactions to
those described in the fifth to seventh paragraphs of the portion of Note [8] immediately above
25 that is concerned with the preparation of starting materials. There was thus obtained 7-(2-acetoxy-3-piperidinopropoxy)-4-chloro-6-methoxyquinazoline; NMR Spectrum: ($CDCl_3$ and CD_3CO_2D) 1.6 (m, 2H), 1.9 (m, 4H), 2.1 (s, 3H), 3.2 (br s, 4H), 3.5 (m, 2H), 4.05 (s, 3H), 4.35 (m, 2H), 5.7 (m, 1H), 7.4 (s, 1H), 7.5 (s, 1H), 8.9 (s, 1H).

- 58 -

Example 3**4-(6-chlorobenzofuran-7-ylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline**

The sodium salt of 1,1,1,3,3,3-hexamethyldisilazane (1M solution in THF; 0.592 ml) was added to a solution of 7-amino-6-chlorobenzofuran (0.099 g) in DMF (5 ml) and the reaction mixture was stirred at ambient temperature for 30 minutes. 4-Chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (0.1 g) was added and the resultant mixture was stirred at ambient temperature for 3 hours. The mixture was partitioned between ethyl acetate and water. The organic phase was washed in turn with water and brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. The material so obtained was dissolved in methylene chloride and a 5M solution of hydrogen chloride gas in isopropanol (0.088 ml) was added. Diethyl ether was added and the precipitate was isolated and dried under vacuum. There was thus obtained the title compound (0.118 g) as a dihydrochloride salt; NMR Spectrum: (DMSO_{d6} and CF₃CO₂D) 2.35 (m, 2H), 3.15 (m, 2H), 3.35 (m, 2H), 3.55 (d, 2H), 3.75 (t, 2H), 4.0 (m, 2H), 4.05 (s, 3H), 4.35 (t, 2H), 7.15 (d, 1H), 7.45 (s, 1H), 7.55 (d, 1H), 7.8 (d, 1H), 8.1 (d, 1H), 8.25 (s, 1H), 8.8 (s, 1H); Mass Spectrum: M+H⁺ 469.

The 7-amino-6-chlorobenzofuran used as a starting material was prepared as follows :-

Sodium hydride (60% dispersion in mineral oil; 4.6 g) was added to a stirred solution of 6-chloroanthranilic acid (18 g) in DMF (100 ml) and the mixture was stirred at ambient temperature for 30 minutes. Ethyl iodide (10 ml) was added and the reaction mixture was stirred at ambient temperature for 2 days. The solvent was evaporated and the residue was partitioned between ethyl acetate and water. The organic phase was washed in turn with water and brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 4:1 mixture of petroleum ether (b.p. 60-80°C) and ethyl acetate as eluent. There was thus obtained ethyl 6-chloroanthranilate (15.8 g) as an oil; NMR Spectrum: (DMSO_{d6}) 1.3 (t, 3H), 4.3 (q, 2H), 5.7 (br s, 2H), 6.6 (d, 1H), 6.7 (d, 1H), 7.1 (t, 1H).

A solution of sodium nitrite (4.5 g) in water (100 ml) was added dropwise during 5 minutes to a stirred suspension of ethyl 6-chloroanthranilate (12.7 g) in a mixture of concentrated sulphuric acid (27.9 ml), water (38 ml) and ice (76 g). The reaction mixture was stirred at 0°C for an additional 20 minutes and then heated to 120°C for 1 hour. The resultant

- 59 -

mixture was poured into a mixture of ice and water and the product was extracted with diethyl ether. The organic phase was washed in turn with water and brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 4:1 mixture of petroleum ether (b.p. 60-80°C) and methylene chloride as eluent. There was
5 thus obtained ethyl 6-chloro-2-hydroxybenzoate (9.8 g); NMR Spectrum: (DMSO-d₆) 1.3 (t, 3H), 4.3 (q, 2H), 6.9 (d, 1H), 6.95 (d, 1H), 7.25 (d, 1H), 10.45 (br s, 1H).

Allyl bromide (5.5 ml) was added to a stirred mixture of ethyl 6-chloro-2-hydroxybenzoate (9.8 g), 1,5,7-triazabicyclo[4,4,0]dec-5-ene (10.4 g) and acetonitrile (250 ml) and the reaction mixture was stirred at ambient temperature for 20 hours. The
10 mixture was evaporated and the residue was purified by column chromatography on silica using a 17:3 mixture of petroleum ether (b.p. 60-80°C) and diethyl ether as eluent. There was thus obtained ethyl 2-allyloxy-6-chlorobenzoate (10.3 g); NMR Spectrum: (DMSO-d₆) 1.3 (t, 3H), 4.35 (q, 2H), 4.65 (d, 2H), 5.25 (d, 1H), 5.4 (d, 1H), 6.0 (m, 1H), 7.15 (m, 2H), 7.45 (t, 1H).

15 The material so obtained was heated to 230°C for 1 hour. The reaction product was cooled to ambient temperature and purified by column chromatography on silica using a 4:1 mixture of petroleum ether (b.p. 60-80°C) and methylene chloride as eluent. There was thus obtained ethyl 3-allyl-6-chloro-2-hydroxybenzoate (7.3 g); NMR Spectrum: (DMSO-d₆) 1.3 (t, 3H), 3.3 (m, 2H), 4.35 (q, 2H), 5.05 (m, 2H), 5.95 (m, 1H), 6.95 (d, 1H), 7.15 (d, 1H), 9.7 (br
20 s, 1H).

Using analogous procedures to those described in the third paragraph of the portion of Note [6] in Example 2 that is concerned with the preparation of 7-amino-5-fluorobenzofuran, ethyl 3-allyl-6-chloro-2-hydroxybenzoate was reacted with ozone and the resultant product, 2-(4-chloro-3-ethoxycarbonyl-2-hydroxyphenyl)acetaldehyde, was treated with 85%
25 phosphoric acid to give ethyl 6-chlorobenzofuran-7-carboxylate (5.9 g); NMR Spectrum: (DMSO-d₆) 1.35 (t, 3H), 4.45 (q, 2H), 7.10 (d, 1H), 7.45 (d, 1H), 7.85 (d, 1H), 8.15 (d, 1H).

A mixture of the material so obtained, 35% aqueous potassium hydroxide solution (12.7 ml) and methanol (20 ml) was stirred and heated to reflux for 1 hour. The methanol was evaporated and the residue was diluted with water and acidified to pH1 by the addition of
30 6N aqueous hydrochloric acid. The resultant precipitate was isolated, washed with water and dried under vacuum over phosphorus pentoxide to give 6-chlorobenzofuran-7-carboxylic acid (4.6 g); NMR Spectrum: (DMSO-d₆) 7.05 (d, 1H), 7.4 (d, 1H), 7.75 (d, 1H), 8.1 (d, 1H).

- 60 -

A mixture of a portion (1 g) of the material so obtained, diphenylphosphoryl azide (2.2 ml), triethylamine (1.4 ml) and tert-butanol (2.7 ml) was stirred and heated to reflux for 18 hours. The mixture was allowed to cool to ambient temperature, poured into water and extracted with ethyl acetate. The organic phase was washed in turn with water and brine, 5 dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on alumina using increasingly polar solvent mixtures starting with mixtures of petroleum ether and methylene chloride and ending with a 4:1 mixture of methylene chloride and ethyl acetate. There was thus obtained a mixture of 7-amino-6-chlorobenzofuran and tert-butyl 6-chlorobenzofuran-7-carbamate. A solution of the mixture so obtained in 10 methylene chloride (15 ml) was cooled to 0°C and trifluoroacetic acid (1.2 ml) was added. The resultant mixture was stirred for 1 hour. The mixture was evaporated and the residue was partitioned between ethyl acetate and a saturated aqueous sodium bicarbonate solution. The organic phase was dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 3:1 mixture of petroleum ether (b.p. 60-80°C) 15 and methylene chloride as eluent. There was thus obtained 7-amino-6-chlorobenzofuran (0.376 g); NMR Spectrum: (DMSO_d₆) 5.5 (br s, 2H), 6.85 (m, 2H), 7.1 (d, 1H), 7.95 (d, 1H); Mass Spectrum: M+H⁺ 167.

Example 4

20 4-(6-chlorobenzofuran-7-ylamino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline

Using an analogous procedure to that described in Example 3, 4-chloro-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline was reacted with 7-amino-6-chlorobenzofuran to give the title compound in 32% yield as a dihydrochloride 25 salt; NMR Spectrum: (DMSO_d₆ and CF₃COOD) 2.35 (m, 2H), 2.9 (s, 3H), 3.4 (br s, 5H), 3.8 (br s, 5H), 4.05 (s, 3H), 4.35 (m, 2H), 7.15 (d, 1H), 7.45 (s, 1H), 7.6 (d, 1H), 7.8 (d, 1H), 8.1 (d, 1H), 8.3 (s, 1H), 8.85 (s, 1H); Mass Spectrum: M+H⁺ 482.

Example 5**4-(3-bromo-6-chlorobenzofuran-7-ylamino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline**

Using an analogous procedure to that described in Example 3,

- 5 4-chloro-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline was reacted with 7-amino-3-bromo-6-chlorobenzofuran to give the title compound in 46% yield as a dihydrochloride salt; NMR Spectrum: (DMSO_d₆ and CF₃COOD) 1.9 (m, 2H), 2.05 (m, 2H), 2.3 (m, 2H), 3.1 (m, 2H), 3.4 (m, 2H), 3.65 (m, 2H), 4.05 (s, 3H), 4.35 (m, 2H), 7.4 (s, 1H), 7.7 (m, 2H), 8.25 (s, 1H), 8.4 (s, 1H), 8.85 (s, 1H); Mass Spectrum: M+H⁺ 530 and 532.

- 10 The 7-amino-3-bromo-6-chlorobenzofuran used as a starting material was prepared as follows:-

- A mixture of 6-chlorobenzofuran-7-carboxylic acid (0.5 g), diphenylphosphoryl azide (0.58 ml), triethylamine (0.39 ml) and tert-butanol (1.4 ml) was stirred and heated to 95°C for 6 hours. The mixture was cooled to ambient temperature and poured into water. The
15 precipitate was isolated, washed with water and dried under vacuum over phosphorus pentoxide. There was thus obtained tert-butyl 6-chlorobenzofuran-7-carbamate (0.665 g); NMR Spectrum: (DMSO_d₆) 1.45 (s, 9H), 7.0 (d, 1H), 7.35 (d, 1H), 7.55 (d, 1H), 8.05 (d, 1H), 9.0 (br s, 1H).

- The material so obtained was dissolved in carbon disulfide (6 ml) and the solution was
20 cooled to -10°C. A solution of bromine (0.11 ml) in carbon disulfide (0.5 ml) was added dropwise. The reaction mixture was stirred and allowed to warm to 15°C. The reaction mixture was filtered and the filtrate was evaporated. There was thus obtained to give a gum containing a mixture of the *cis*- and *trans*- isomers of tert-butyl 2,3-dibromo-6-chloro-2,3-dihydrobenzofuran-7-carbamate (0.87 g).

- 25 The material so obtained was dissolved in ethanol (35 ml) and the solution was cooled to 0°C. A 0.8N aqueous potassium hydroxide solution (23 ml) was added and the reaction mixture was stirred at ambient temperature for 1.5 hours. The mixture was concentrated by evaporation, water was added and the mixture was neutralised by the addition of 6N aqueous hydrochloric acid. The mixture was extracted with diethyl ether. The organic phase was
30 washed with water and with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 3:2 mixture of petroleum ether (b.p. 60-80°C) and methylene chloride as eluent. There was thus obtained tert-butyl

- 62 -

3-bromo-6-chlorobenzofuran-7-carbamate (0.325 g); NMR Spectrum: (DMSO_d₆) 1.45 (s, 9H), 7.45 (d, 1H), 7.5 (d, 1H), 8.4 (s, 1H), 9.1 (br s, 1H); Mass Spectrum: M+H⁺ 347.

A solution of the material so obtained in methylene chloride (5 ml) was cooled to 0°C and trifluoroacetic acid (0.65 ml) was added. The resultant mixture was allowed to warm to ambient temperature and was stirred for 6 hours. The mixture was evaporated, water was added and the mixture was basified to pH 7.5 by the addition of a saturated aqueous sodium bicarbonate solution. The resultant mixture was extracted with diethyl ether. The organic phase was washed in turn with water and brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 3:2 mixture of petroleum ether (b.p. 60-80°C) and methylene chloride as eluent. There was thus obtained 7-amino-3-bromo-6-chlorobenzofuran (0.15 g); NMR Spectrum: (DMSO_d₆) 5.8 (br s, 2H), 6.7 (d, 1H), 7.2 (d, 1H), 8.3 (s, 1H); Mass Spectrum: M+H⁺ 247.

The 4-chloro-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline used as a starting material was prepared as follows :-

A mixture of 4-hydroxy-3-methoxybenzoic acid (8.4 g), 3-(pyrrolidin-1-yl)propyl chloride (*J. Amer. Chem. Soc.*, 1955, 77, 2272; 14.75 g), potassium carbonate (13.8 g), potassium iodide (1.66 g) and DMF (150 ml) was stirred and heated to 100°C for 3 hours. The mixture was allowed to cool to ambient temperature, filtered and the filtrate was evaporated. The residue was dissolved in ethanol (75 ml), 2N aqueous sodium hydroxide solution (75 ml) was added and the mixture was heated to 90°C for 2 hours. The mixture was concentrated by evaporation and acidified by the addition of concentrated aqueous hydrochloric acid. The resultant mixture was washed with diethyl ether and then purified by column chromatography using a Diaion (trade mark of Mitsubishi) HP20SS resin column, eluting with water and then with a gradient of methanol (0 to 25%) in dilute hydrochloric acid (pH2.2). The methanol was removed by evaporation and the aqueous residue was freeze dried to give 3-methoxy-4-(3-pyrrolidin-1-ylpropoxy)benzoic acid hydrochloride (12.2 g); NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 2.2 (m, 2H), 3.15 (t, 2H), 3.3 (t, 2H), 3.5 (d, 2H), 3.7 (t, 2H), 3.82 (s, 3H), 4.05 (d, 2H), 4.15 (t, 2H), 7.07 (d, 1H), 7.48 (s, 1H), 7.59 (d, 1H).

The material so obtained was dissolved in trifluoroacetic acid (40 ml) and the solution was cooled to 0°C. Fuming nitric acid (2.4 ml) was added slowly. The cooling bath was removed and the reaction mixture was stirred at ambient temperature for 1 hour. The mixture was evaporated and a mixture of ice and water was added to the residue. The mixture was

- 63 -

evaporated. The solid residue was dissolved in dilute hydrochloric acid (pH2.2) and purified by column chromatography using a Diaion HP20SS resin column using a gradient of methanol (0 to 50%) in water. Concentration of the fractions by evaporation gave a precipitate which was collected and dried under vacuum over phosphorus pentoxide. There was thus obtained

5 5-methoxy-2-nitro-4-(3-pyrrolidin-1-ylpropoxy)benzoic acid hydrochloride (12.1 g, 90%);
NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.8-1.9 (m, 2H), 2.0-2.1 (m, 2H), 2.1-2.2 (m, 2H), 3.0-3.1 (m, 2H), 3.3 (t, 2H), 3.6-3.7 (m, 2H), 3.95 (s, 3H), 4.25 (t, 2H), 7.35 (s, 1H), 7.62 (s, 1H).

A mixture of a portion (9.63 g) of the material so obtained, thionyl chloride (20 ml)

10 and DMF (0.05 ml) was heated to 45°C for 1.5 hours. The excess thionyl chloride was evaporated using the evaporation of added toluene (x2) to remove the last traces. The resultant solid was suspended in a mixture of THF (250 ml) and methylene chloride (100ml) and ammonia was bubbled through the mixture for 30 minutes. The resultant mixture was stirred for a further 1.5 hours at ambient temperature. The volatiles were removed by

15 evaporation and the residue was dissolved in water and purified by column chromatography using a Diaion HP20SS resin column eluting with a gradient of methanol (0 to 5%) in water. The solvent was removed by evaporation from the fractions containing product. The residue was dissolved in a minimum of methanol and the solution was diluted with diethyl ether. The resultant precipitate was collected by filtration, washed with diethyl ether and dried under

20 vacuum to give 5-methoxy-2-nitro-4-(3-pyrrolidin-1-ylpropoxy)benzamide (7.23 g); NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.85-1.95 (m, 2H), 2-2.1 (m, 2H), 2.15-2.25 (m, 2H), 3.0-3.1 (m, 2H), 3.31 (t, 2H), 3.62 (t, 2H), 3.93 (s, 3H), 4.2 (t, 2H), 7.16 (s, 1H), 7.6 (s, 1H).

A mixture of a portion (1.5 g) of the material so obtained, concentrated aqueous hydrochloric acid (5 ml) and methanol (20 ml) was warmed to 50°C to give a solution. Iron

25 powder (1.3 g) was added in portions and the reaction mixture was heated to reflux for 1 hour. The mixture was allowed to cool to ambient temperature. Insoluble material was removed by filtration through diatomaceous earth and the filtrate was evaporated. The residue was purified by column chromatography using a Diaion HP20SS resin column, eluting with water and then with dilute aqueous hydrochloric acid (pH2). The fractions containing product were

30 concentrated by evaporation and the resultant precipitate was collected by filtration and dried under vacuum over phosphorus pentoxide. There was thus obtained 2-amino-5-methoxy-4-(3-pyrrolidin-1-ylpropoxy)benzamide hydrochloride (1.44 g); NMR Spectrum: (DMSO_d₆

- 64 -

and $\text{CF}_3\text{CO}_2\text{D}$) 1.9 (br s, 2H), 2.05 (br s, 2H), 2.2 (br s, 2H), 3.05 (br s, 2H), 3.3 (t, 2H), 3.61 (br s, 2H), 3.8 (s, 3H), 4.11 (t, 2H), 7.05 (s, 1H), 7.53 (s, 1H).

After repetition of the previous reaction, a mixture of 2-amino-5-methoxy-4-(3-pyrrolidin-1-ylpropoxy)benzamide hydrochloride (5.92 g), Gold's reagent (3.5 g) and dioxane (50 ml) was heated to reflux for 5 hours. Acetic acid (0.7 ml) and sodium acetate (1.33 g) were added and the reaction mixture was heated to reflux for a further 5 hours. The mixture was allowed to cool to ambient temperature and evaporated. The residue was dissolved in water, adjusted to pH8 with 2N aqueous sodium hydroxide solution and purified on a Diaion HP20SS resin column eluting with methanol (gradient 0-50 %) in water. The fractions containing product were concentrated by evaporation and then freeze dried to give 6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)-3,4-dihydroquinazolin-4-one (4.55 g); NMR Spectrum: (DMSO-d_6 and $\text{CF}_3\text{CO}_2\text{D}$) 1.9 (m, 2H), 2.0-2.1 (m, 2H), 2.2-2.3 (m, 2H), 3.05 (m, 2H), 3.34 (t, 2H), 3.6-3.7 (br s, 2H), 3.94 (s, 3H), 4.27 (t, 2H), 7.31 (s, 1H), 7.55 (s, 1H), 9.02 (s, 1H).

A mixture of a portion (1.7 g) of the material so obtained, thionyl chloride (25 ml) and DMF (0.2 ml) was heated at reflux for 3 hours. Excess thionyl chloride was removed by evaporation and by azeotropeing with toluene (x2). The residue was suspended in diethyl ether and washed with a 10% aqueous solution of sodium bicarbonate. The organic layer was dried over magnesium sulphate and evaporated to give 4-chloro-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (1.94 g); NMR Spectrum: (CDCl_3) 1.8 (br s, 4H), 2.17 (m, 2H), 2.6 (br s, 4H), 2.7 (t, 2H), 4.05 (s, 3H), 4.3 (t, 2H), 7.35 (s, 1H), 7.38 (s, 1H), 8.86 (s, 1H).

Example 6

4-(3-chlorobenzofuran-7-ylamino)-7-(2-hydroxy-3-morpholinopropoxy)-6-methoxyquinazoline dihydrochloride salt

A mixture of 7-(2-acetoxy-3-morpholinopropoxy)-4-(3-chlorobenzofuran-7-ylamino)-6-methoxyquinazoline dihydrochloride (0.15 g) and a saturated methanolic ammonia solution (3 ml) was stirred at ambient temperature overnight. The solvent was evaporated and the residue was dissolved in methylene chloride (3 ml) and adsorbed to the top of a pre-packed silica column (NH_2 -silica; Isolute sorbent from International Sorbent Technology Ltd, ref. no. 9470-0100) and eluted with a 19:1 mixture of methylene chloride and methanol. The material so obtained was dissolved in methylene chloride (3 ml) and a 6M solution of hydrogen

- 65 -

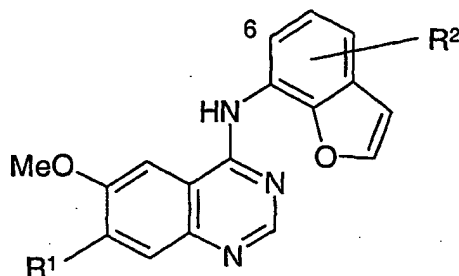
chloride in isopropanol (0.3ml) was added. Diethyl ether (10 ml) was added and the resultant precipitate was collected by filtration, washed with diethyl ether and dried under vacuum.

There was thus obtained the title compound (0.11 g); Mass Spectrum: $M+H^+$ 486.

5 Example 7

Using an analogous procedure to that described in Example 6, the appropriate 7-(2-acetoxypoxy)quinazoline was reacted with a saturated methanolic ammonia solution to give the compounds described in Table II. Unless otherwise stated, each compound described in Table II was obtained as a dihydrochloride salt.

Table II



No.	R ¹	R ²	Note
1	2-hydroxy-3-(N-isopropyl-N-methylamino)propoxy	3-chloro	[1]
2	3-(4-cyanomethylpiperazin-1-yl)-2-hydroxypropoxy	3-chloro	[2]
3	2-hydroxy-3-pyrrolidin-1-ylpropoxy	3-chloro	[3]
4	2-hydroxy-3-piperidinopropoxy	3-chloro	[4]

Notes

- 15 [1] The product gave the following characterising data: NMR Spectrum: (DMSO_d₆ and CF₃CO₂D): 1.21-1.37 (m, 6H), 2.81 (s, 3H), 3.12-3.5 (m, 2H), 3.56-3.74 (m, 1H), 4.05 (s, 3H), 4.33-4.32 (m, 2H), 4.4-4.5 (m, 1H), 7.46 (d, 1H), 7.55 (t, 1H), 7.6 (d, 1H), 7.71 (m, 1H), 8.29 (s, 1H), 8.38 (s, 1H), 8.84 (s, 1H); Mass Spectrum: $M+H^+$ 471.

- [2] The product gave the following characterising data: NMR Spectrum: (DMSO_d₆ and
 20 CF₃CO₂D): 2.64-2.88 (m, 2H), 2.89-3.1 (m, 2H), 3.13-3.48 (m, 4H), 3.54-3.74 (m, 2H), 3.88 (s, 2H), 4.05 (s, 3H), 4.21-4.32 (m, 2H), 4.48-4.58 (m, 1H), 7.51 (s, 1H), 7.54 (t, 1H), 7.6 (m, 1H), 7.7 (m, 1H), 8.36 (s, 1H), 8.38 (s, 1H), 8.83 (s, 1H); Mass Spectrum: $M+H^+$ 523.

- 66 -

- [3] The product gave the following characterising data: NMR Spectrum: (DMSO_d₆ and CF₃CO₂D): 1.87-1.99 (m, 2H), 2.0-2.1 (m, 2H), 3.1-3.22 (m, 2H), 3.4 (d, 2H), 3.6-3.7 (m, 2H), 4.04 (s, 3H), 4.25 (d, 2H), 4.35-4.45 (m, 1H), 7.45 (s, 1H), 7.54 (t, 1H), 7.60 (m, 1H), 7.71 (m, 1H), 8.28 (s, 1H), 8.38 (s, 1H), 8.84 (s, 1H); Mass Spectrum: M+H⁺ 469.
- 5 [4] The product gave the following characterising data: NMR Spectrum: (DMSO_d₆ and CF₃CO₂D): 1.36-1.52 (m, 1H), 1.66-1.93 (m, 5H), 2.93-3.13 (m, 2H), 3.21-3.4 (m, 2H), 3.48-3.64 (m, 2H), 4.06 (s, 3H), 4.26 (d, 2H), 4.48-4.59 (m, 1H), 7.5 (s, 1H), 7.54 (t, 1H), 7.6 (m, 1H), 7.7 (m, 1H), 8.34 (s, 1H), 8.37 (s, 1H), 8.84 (s, 1H); Mass Spectrum: M+H⁺ 483.

10 Example 8

4-(6-chlorobenzofuran-7-ylamino)-6-methoxy-7-piperidin-4-ylmethoxyquinazoline

A mixture of 7-(N-tert-butoxycarbonylpiperidin-4-ylmethoxy)-4-(6-chlorobenzofuran-7-ylamino)-6-methoxyquinazoline (0.4 g), trifluoroacetic acid (3 ml) and methylene chloride (12 ml) was stirred at ambient temperature for 3 hours. The mixture was evaporated and the
15 residue was diluted with water. The mixture was basified to pH11 by the addition of 1 N aqueous sodium hydroxide solution and methylene chloride was added. The precipitate which was formed was collected by filtration, washed with water and dried under vacuum to give the title compound (0.195 g); NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.55 (m, 2H), 2.0 (m, 2H), 2.25 (m, 1H), 2.95 (m, 2H), 3.4 (m, 2H), 4.05 (s, 3H), 4.2 (d, 2H), 7.1 (d, 1H), 7.4 (s,
20 1H), 7.55 (d, 1H), 7.8 (d, 1H), 8.05 (d, 1H), 8.2 (s, 1H), 8.85 (s, 1H), Mass Spectrum: M-H 437.

The 7-(N-tert-butoxycarbonylpiperidin-4-ylmethoxy)-4-(6-chlorobenzofuran-7-ylamino)-6-methoxyquinazoline used as a starting material was prepared as follows:

The sodium salt of 1,1,1,3,3,3-hexamethyldisilazane (66 ml, 1M solution in THF) was
25 added dropwise to 7-amino-6-chlorobenzofuran (11.0 g) in solution in DMF (170 ml) and the mixture was stirred at ambient temperature for 30 minutes. A solution of 7-benzyloxy-4-chloro-6-methoxyquinazoline (9.8 g) in DMF (200 ml) was added and the reaction mixture was stirred at ambient temperature for 24 hours. The solvent was evaporated and the residue was partitioned between methylene chloride and water. The organic phase was washed with
30 water and with brine, dried over magnesium sulphate and evaporated. The material so obtained was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol. There was thus obtained 7-benzyloxy-

- 67 -

4-(6-chlorobenzofuran-7-ylamino)-6-methoxyquinazoline (12.0 g) as a solid; NMR Spectrum: (DMSO-d₆) 3.95 (s, 3H), 5.3 (s, 2H), 7.05 (s, 1H), 7.3 (s, 1H), 7.35-7.55 (m, 6H), 7.65 (d, 1H), 7.95 (s, 1H), 8.0 (d, 1H), 8.25 (s, 1H), 9.75 (s, 1H); Mass Spectrum: M+H⁺ 432 and 434.

A mixture of the material so obtained and trifluoroacetic acid (120 ml) was heated to
5 reflux for 5 hours. The solvent was evaporated, toluene was added and the solvent was
evaporated again. The residue was diluted with water and the pH was adjusted to 8 with a
saturated aqueous solution of sodium bicarbonate. Methylene chloride (150 ml) was added
which caused the desired product to precipitate. The solid was collected by filtration, washed
with water and dried under vacuum to give the 4-(6-chlorobenzofuran-7-ylamino)-7-hydroxy-
10 6-methoxyquinazoline (9.5 g); NMR Spectrum: (DMSO-d₆) 4.0 (s, 3H), 7.1 (s, 1H), 7.15 (s,
1H), 7.5 (d, 1H), 7.7 (d, 1H), 8.0 (m, 2H), 8.4 (br s, 1H); Mass Spectrum: M+H⁺ 342.

N-(tert-Butoxycarbonyl)-4-(4-toluenesulphonyloxymethyl)piperidine (0.388 g) was
added to a mixture of 4-(6-chlorobenzofuran-7-ylamino)-7-hydroxy-6-methoxyquinazoline
(0.3 g), potassium carbonate (0.484 g) and DMF (4 ml) and the mixture was heated to 55°C
15 for 4 hours and to 80°C for 3 hours. The excess potassium carbonate was removed by
filtration. The filtrate was evaporated and the residue was partitioned between ethyl acetate
and water. The organic phase was washed with water and with brine, dried over magnesium
sulphate and evaporated. The material so obtained was purified by column chromatography
on silica using increasingly polar mixtures of methylene chloride and methanol as eluent.
20 There was thus obtained 7-(N-tert-butoxycarbonylpiperidin-4-ylmethoxy)-
4-(6-chlorobenzofuran-7-ylamino)-6-methoxyquinazoline (0.405 g); Mass Spectrum:
M-H 537.

The N-tert-butoxycarbonyl-4-(4-toluenesulphonyloxymethyl)piperidine used as a
starting material was prepared as follows :-

25 A solution of di-tert-butyl dicarbonate (41.7 g) in ethyl acetate (75 ml) was added
dropwise to a stirred solution of ethyl piperidine-4-carboxylate (30 g) in ethyl acetate (150 ml)
which had been cooled to 0 to 5°C in an ice-bath. The resultant mixture was stirred at
ambient temperature for 48 hours. The mixture was poured into water (300 ml). The organic
layer was separated, washed in turn with water (200 ml), 0.1N aqueous hydrochloric acid
30 solution (200 ml), a saturated aqueous sodium bicarbonate solution (200 ml) and brine
(200 ml), dried over magnesium sulphate and evaporated. There was thus obtained ethyl
N-tert-butoxycarbonylpiperidine-4-carboxylate (48 g); NMR Spectrum: (CDCl₃) 1.25 (t, 3H),

- 68 -

1.45 (s, 9H), 1.55-1.7 (m, 2H), 1.8-2.0 (d, 2H), 2.35-2.5 (m, 1H), 2.7-2.95 (t, 2H), 3.9-4.1 (br s, 2H), 4.15 (q, 2H).

A solution of the material so obtained in THF (180 ml) was cooled at 0°C and lithium aluminium hydride (1M solution in THF; 133 ml) was added dropwise. The mixture was stirred at 0°C for 2 hours. Water (30 ml) and 2N aqueous sodium hydroxide solution (10 ml) were added in turn and the mixture was stirred for 15 minutes. The resultant mixture was filtered through diatomaceous earth and the solids were washed with ethyl acetate. The filtrate was washed in turn with water and with brine, dried over magnesium sulphate and evaporated. There was thus obtained N-tert-butoxycarbonyl-4-hydroxymethylpiperidine (36.3 g); NMR Spectrum: (CDCl₃) 1.05-1.2 (m, 2H), 1.35-1.55 (m, 10H), 1.6-1.8 (m, 2H), 2.6-2.8 (t, 2H), 3.4-3.6 (t, 2H), 4.0-4.2 (br s, 2H).

1,4-Diazabicyclo[2.2.2]octane (42.4 g) was added to a solution of N-tert-butoxycarbonyl-4-hydroxymethylpiperidine (52.5 g) in tert-butyl methyl ether (525 ml) and the mixture was stirred at ambient temperature for 15 minutes. The mixture was then cooled in an ice-bath to 5°C and a solution of 4-toluenesulphonyl chloride (62.8 g) in tert-butyl methyl ether (525 ml) was added dropwise over 2 hours while maintaining the reaction temperature at approximately 0°C. The resultant mixture was allowed to warm to ambient temperature and was stirred for 1 hour. Petroleum ether (b.p. 60-80°C, 1L) was added and the precipitate was removed by filtration. The filtrate was evaporated to give a solid residue which was dissolved in diethyl ether. The organic solution was washed in turn with 0.5N aqueous hydrochloric acid solution, water, a saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and evaporated. There was thus obtained N-tert-butoxycarbonyl-4-(4-toluenesulphonyloxymethyl)piperidine (76.7 g); NMR Spectrum: (CDCl₃) 1.0-1.2 (m, 2H), 1.45 (s, 9H), 1.65 (d, 2H), 1.75-1.9 (m, 2H), 2.45 (s, 3H), 2.55-2.75 (m, 2H), 3.85 (d, 1H), 4.0-4.2 (br s, 2H), 7.35 (d, 2H), 7.8 (d, 2H).

Example 9

4-(6-chlorobenzofuran-7-ylamino)-6-methoxy-7-(1-methylpiperazin-4-ylmethoxy)quinazoline

(6-Chlorobenzofuran-7-ylamino)-6-methoxy-7-piperidin-4-ylmethoxyquinazoline (0.22 g) was dissolved in methylene chloride (17 ml). Formaldehyde (37% aqueous solution; 0.089 ml) and sodium triacetoxyborohydride (0.149 g) were added in turn followed by

- 69 -

methanol (5 ml). The reaction mixture was stirred at ambient temperature for 1 hour. A saturated aqueous solution of sodium bicarbonate (10 ml) was added and the product was extracted with methylene chloride. The organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated. The crude product was purified by column chromatography on silica using increasingly polar solvent mixtures of methylene chloride and a saturated methanolic ammonia solution. The material so obtained was triturated under diethyl ether. There was thus obtained the title compound; NMR Spectrum: (DMSO-d₆) 1.5 (m, 2H), 1.9 (m, 3H), 2.4 (m, 5H), 3.1 (m, 2H), 3.95 (s, 3H), 4.05 (d, 2H), 7.05 (d, 1H), 7.2 (s, 1H), 7.45 (d, 1H), 7.65 (d, 1H), 7.9 (s, 1H), 8.0 (s, 1H), 8.25 (s, 1H), 9.75 (s, 1H); Mass Spectrum: M+H⁺ 453.

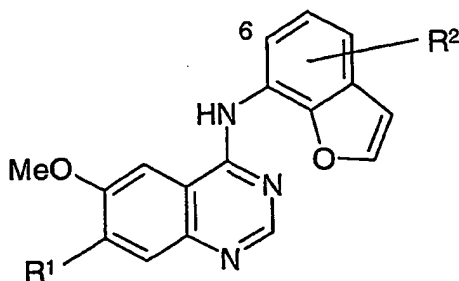
Example 10

4-(6-chlorobenzofuran-7-ylamino)-6-methoxy-7-(2-pyrrolidin-1-ylethoxy)quinazoline

Diethyl azodicarboxylate (0.101 ml) was added dropwise to a stirred mixture of 4-(6-chlorobenzofuran-7-ylamino)-7-hydroxy-6-methoxyquinazoline (0.1 g), 1-(2-hydroxyethyl)pyrrolidine (0.04 g), triphenylphosphine (0.169 g) and methylene chloride (5 ml) and the reaction mixture was stirred at ambient temperature for 2 hours. The solvent was evaporated and the residue was purified by column chromatography on silica using increasingly polar mixture of methylene chloride and a saturated methanolic ammonia solution as eluent. There was thus obtained the title compound (0.033 g) as a solid; NMR Spectrum: (DMSO-d₆ and CF₃CO₂D) 1.9 (m, 2H), 2.1 (m, 2H), 3.2 (m, 2H), 3.65-3.85 (m, 4H), 4.05 (s, 3H), 4.6 (m, 2H), 7.15 (d, 1H), 7.45 (s, 1H), 7.6 (d, 1H), 7.8 (d, 1H), 8.1 (d, 1H), 8.25 (s, 1H), 8.85 (s, 1H); Mass Spectrum: M+H⁺ 439.

Example 11

Using an analogous procedure to that described in Example 10, the appropriate alcohol was reacted with 4-(6-chlorobenzofuran-7-ylamino)-7-hydroxy-6-methoxyquinazoline to give the compounds described in Table III.

Table III

No.	R ¹	R ²	Note
1	3-pyrrolidin-1-ylpropoxy	6-chloro	[1]
2	2-piperidinoethoxy	6-chloro	[2]
3	2-(4-methylpiperazin-1-yl)ethoxy	6-chloro	[3]

Notes

- 10 [1] The product gave the following characterising data: NMR Spectrum: (DMSO-d₆ and CF₃CO₂D) 1.9 (m, 2H), 2.05 (m, 2H), 2.25 (m, 2H), 3.1 (m, 2H), 3.35 (m, 2H), 3.65 (m, 2H), 4.05 (s, 3H), 4.35 (m, 2H), 7.15 (d, 1H), 7.4 (s, 1H), 7.55 (d, 1H), 7.8 (d, 1H), 8.05 (d, 1H), 8.2 (s, 1H), 8.8 (s, 1H); Mass Spectrum: M-H⁺ 451.
- 15 [2] The product gave the following data: NMR Spectrum: (DMSO-d₆ and CF₃CO₂D) 1.4 (m, 1H), 1.7 (m, 3H), 1.9 (m, 2H), 3.1 (m, 2H), 3.6 (m, 2H), 3.7 (m, 2H), 4.05 (s, 3H), 4.65 (t, 2H), 7.15 (d, 1H), 7.45 (s, 1H), 7.6 (d, 1H), 7.8 (d, 1H), 8.1 (d, 1H), 8.25 (s, 1H), 8.85 (s, 1H); Mass Spectrum: M-H⁺ 451.
- 20 [3] The product gave the following characterising data: NMR Spectrum: (DMSO-d₆ and CF₃CO₂D) 2.9 (s, 3H), 3.3-3.9 (m, 10H), 4.05 (s, 3H), 4.6 (m, 2H), 7.15 (d, 1H), 7.5 (s, 1H), 7.6 (d, 1H), 7.8 (d, 1H), 8.1 (d, 1H), 8.25 (s, 1H), 8.85 (s, 1H); Mass Spectrum: M-H⁺ 466.

Example 12**4-(6-chlorobenzofuran-7-ylamino)-7-[(2R)-2-hydroxy-3-piperidinopropoxy]-
6-methoxyquinazoline dihydrochloride salt**

A mixture of 4-(6-chlorobenzofuran-7-ylamino)-7-[(2R)-2,3-epoxypropoxy]-
5 6-methoxyquinazoline (0.1 g), piperidine (2.5 mole equivalents), chloroform (2.5 ml) and
ethanol (2.5 ml) was heated to 40°C for 8 hours. The solvent was evaporated under reduced
pressure. Methylene chloride (5 ml) was added followed by a polystyrene isocyanate resin
(0.3 g; loading: 1 mmol/g; prepared according to *J. Amer. Chem. Soc.*, 1997, **119**, 4882) and
the mixture was shaken for 1.5 hours at ambient temperature. The resin was removed by
10 filtration and washed with methylene chloride. The solvent was evaporated and the crude
product was purified by column chromatography on silica using increasingly polar mixture of
methylene chloride and a saturated methanolic ammonia solution as eluent. The material so
obtained was dissolved in a 9:1 mixture (3 ml) of methylene chloride and methanol and a
2.2M solution of hydrogen chloride in diethyl ether (1 ml) was added. The resultant
15 precipitate was collected by filtration and dried under vacuum to give the desired product as a
dihydrochloride salt (0.09 g); NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.35-1.5 (m, 1H),
1.65-1.92 (m, 5H), 2.93-3.13 (m, 2H), 3.21-3.39(m, 2H), 3.48-3.61 (m, 2H), 4.05 (s, 3H), 4.26
(d, 2H), 4.47-4.56 (m, 1H), 7.11 (d, 1H), 7.49 (s, 1H), 7.56 (d, 1H), 7.78 (d, 1H), 8.06 (d, 1H),
8.32 (s, 1H), 8.83(s, 1H); Mass Spectrum: M+H⁺ 483.

20 The 4-(6-chlorobenzofuran-7-ylamino)-7-[(2R)-2,3-epoxypropoxy]-
6-methoxyquinazoline used as a starting material was prepared as follows :-

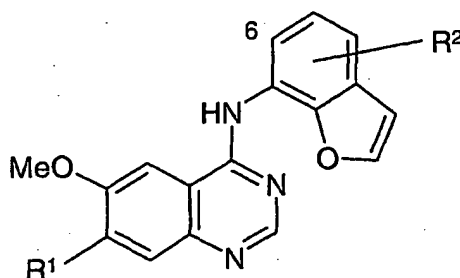
A mixture of 4-(6-chlorobenzofuran-7-ylamino)-7-hydroxy-6-methoxyquinazoline
(5.0 g), (2R)-(-) glycidyl tosylate (4 g), potassium carbonate (8 g) and DMF (60 ml) was
heated to 55°C for 4 hours. The excess potassium carbonate was removed by filtration and
25 washed with ethyl acetate. The combined solvents were evaporated and the residue was
partitioned between a mixture of ethyl acetate and acetonitrile and water. The organic phase
was washed in turn with a 5% aqueous ammonium hydroxide solution, water and brine, dried
over magnesium sulphate and evaporated. The resultant foam was suspended in methylene
chloride and diethyl ether was added to form a precipitate which was collected by filtration
30 and dried under vacuum. There was thus obtained the desired product (4.6 g); NMR
Spectrum: (DMSO_d₆) 2.75 (m, 1H); 2.9 (m, 1H); 3.45 (m, 1H); 4.0 (s, 3H); 4.55 (m, 1H); 7.05

- 72 -

(s, 1H); 7.25 (s, 1H); 7.5 (d, 1H); 7.65 (d, 1H); 7.95 (s, 1H); 8.0 (s, 1H); 8.25 (s, 1H); 9.8 (s, 1H).

Example 13

- 5 Using an analogous procedure to that described in Example 12, the appropriate amine was reacted with 4-(6-chlorobenzofuran-7-ylamino)-7-[(2R)-2,3-epoxypropoxy]-6-methoxyquinazoline to give the compounds described in Table IV.

Table IV

10

No.	R ¹	R ²	Note
1	(2R)-2-hydroxy-3-pyrrolidin-1-ylpropoxy	6-chloro	[1]
2	(2R)-2-hydroxy-3-(N-isopropyl-N-methylamino)propoxy	6-chloro	[2]
3	(2R)-3-(N-allyl-N-methylamino)-2-hydroxypropoxy	6-chloro	[3]
4	(2R)-3-homopiperidin-1-yl-2-hydroxypropoxy	6-chloro	[4]
5	3-[(2S)-2-(N,N-dimethylcarbamoyl)pyrrolidin-1-yl]- (2R)-2-hydroxypropoxy	6-chloro	[5]
6	(2R)-2-hydroxy-3-(N-isobutyl-N-methylamino)propoxy	6-chloro	[6]

Notes

- [1] The product gave the following characterising data; **NMR Spectrum**: (DMSO-d₆ and CF₃CO₂D) 1.86-1.98 (m, 2H), 1.99-2.12 (m, 2H), 3.08-3.21 (m, 2H), 3.34-3.45 (m, 2H), 3.6-
 15 3.71 (m, 2H), 4.06 (s, 3H), 4.26 (d, 2H), 4.37-4.46 (m, 1H), 7.12 (d, 1H), 7.50 (s, 1H), 7.56 (d, 1H), 7.79 (d, 1H), 8.06 (d, 1H), 8.34 (s, 1H), 8.82 (s, 1H); **Mass Spectrum**: M+H⁺ 469.
- [2] The product gave the following characterising data; **NMR Spectrum**: (DMSO-d₆ and CF₃CO₂D) 1.21-1.38 (m, 6H), 2.81(s, 3H), 3.09-3.67(m, 3H), 4.06 (s, 3H), 4.22-4.33 (m, 2H),
 4.38-4.52 (m, 1H), 7.13 (d, 1H), 7.48 (d, 1H), 7.57 (d, 1H), 7.79 (d, 1H), 8.07 (d, 1H), 8.31 (s,
 20 1H); 8.84 (s, 1H); **Mass Spectrum**: M+H⁺ 471.

- 73 -

- [3] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 2.86 (br s, 3H), 3.18-3.46 (m, 2H), 3.75-3.99 (m, 2H), 4.06 (s, 3H), 4.22-4.33 (m, 2H), 4.43-4.57 (m, 1H), 5.5-5.6 (m, 2H), 6.0 (m, 1H), 7.12 (d, 1H), 7.51 (s, 1H), 7.56 (d, 1H), 7.79 (d, 1H), 8.07 (d, 1H), 8.36 (s, 1H), 8.83 (s, 1H); Mass Spectrum: M+H⁺ 469.
- 5 [4] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.54-1.74 (m, 4H), 1.75-1.98 (m, 4H), 3.17-3.34 (m, 3H), 3.38-3.55 (m, 3H), 4.06 (s, 3H), 4.26 (d, 2H), 4.42-4.52 (m, 1H), 7.13 (d, 1H), 7.48 (s, 1H), 7.57 (d, 1H), 7.8 (d, 1H), 8.08 (d, 1H), 8.29 (s, 1H), 8.84 (s, 1H); Mass Spectrum: M+H⁺ 497.
- [5] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and 10 CF₃CO₂D) 1.75-2.0 (m, 2H), 2.06-2.2 (m, 1H), 2.54-2.64 (m, 1H), 2.95 (s, 3H), 3.01 (s, 3H), 3.22-3.37 (m, 2H), 3.46-3.54 (m, 1H), 3.84-3.95 (m, 1H), 4.05 (s, 3H), 4.18-4.3 (m, 2H), 4.39-4.5 (m, 1H), 4.83 (t, 1H), 7.13 (d, 1H), 7.45 (s, 1H), 7.57 (d, 1H), 7.79 (d, 1H), 8.07 (d, 1H), 8.29 (s, 1H), 8.83 (s, 1H); Mass Spectrum: M+H⁺ 540.
- [6] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and 15 CF₃CO₂D) 0.94-1.09 (m, 6H), 2.04-2.26 (m, 1H), 2.95 (s, 3H), 2.96-3.05 (m, 1H), 3.08-3.33 (m, 2H), 3.34-3.47 (m, 1H), 4.07 (s, 3H), 4.21-4.34 (m, 2H), 4.46-4.61 (m, 1H), 7.13 (d, 1H), 7.52 (s, 1H), 7.57 (d, 1H), 7.79 (d, 1H), 8.08 (d, 1H), 8.36 (s, 1H), 8.84 (s, 1H); Mass Spectrum: M+H⁺ 485.

20 Example 14

7-[2-(N-tert-butoxycarbonylpiperidin-4-yl)ethoxy]-4-(6-chlorobenzofuran-7-ylamino)-6-methoxyquinazoline

- Diethyl azodicarboxylate (0.304 ml) was added dropwise to a stirred mixture of 4-(6-chlorobenzofuran-7-ylamino)-7-hydroxy-6-methoxyquinazoline (0.3 g),
- 25 2-(N-tert-butoxycarbonylpiperidin-4-yl)ethanol [International Patent Application WO 00/47212 (within Example 126 thereof); 0.221 g], triphenylphosphine (0.506 g) and methylene chloride (20 ml) and the reaction mixture was stirred at ambient temperature for 3 hours. The solvent was removed by evaporation and the residue was purified by column chromatography on silica using increasingly polar solvent mixtures of methylene chloride and
- 30 acetonitrile. There was thus obtained the title compound (0.49 g); Mass Spectrum: M+H⁺ 553 and 555.

- 74 -

Example 15**4-(6-chlorobenzofuran-7-ylamino)-6-methoxy-7-(2-piperidin-4-ylethoxy)quinazoline**

A mixture of 7-[2-(N-tert-butoxycarbonylpiperidin-4-yl)ethoxy]-4-(6-chlorobenzofuran-7-ylamino)-6-methoxyquinazoline (0.49 g), trifluoroacetic acid (4 ml) and methylene chloride (15 ml) was stirred at ambient temperature for 3 hours. The solvents were evaporated and the residue was diluted with toluene and evaporated again. The residue was partitioned between a mixture of methylene chloride and acetonitrile and a 2N aqueous sodium hydroxide solution. The organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated. The material so obtained was purified by column chromatography using increasingly polar mixtures of methylene chloride and a saturated methanolic ammonia solution. The material so obtained was triturated under diethyl ether to give the title compound (0.296 g); NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.4 (m, 2H), 1.75-1.95 (m, 5H), 2.9 (m, 2H), 3.3 (m, 2H), 4.05 (s, 3H), 4.3 (m, 2H), 7.15 (d, 1H), 7.4 (s, 1H), 7.55 (d, 1H), 7.8 (d, 1H), 8.1 (d, 1H), 8.2 (s, 1H), 8.8 (s, 1H), Mass Spectrum: M+H⁺ 453.

Example 16**4-(6-chlorobenzofuran-7-ylamino)-6-methoxy-7-[2-(N-methylpiperazin-4-yl)ethoxy]quinazoline**

Using an analogous procedure to that described in Example 9, 4-(6-chlorobenzofuran-7-ylamino)-6-methoxy-7-(2-piperidin-4-ylethoxy)quinazoline (0.246 g) was reacted with formaldehyde to give the title compound (0.122 g); NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.45 (m, 2H), 1.8 (m, 3H), 2.0 (m, 2H), 2.8 (s, 3H), 2.95 (m, 2H), 3.45 (m, 2H), 4.05 (s, 3H), 4.3 (t, 2H), 7.15 (d, 1H), 7.4 (s, 1H), 7.6 (d, 1H), 7.8 (d, 1H), 8.1 (d, 1H), 8.2 (s, 1H), 8.85 (s, 1H); Mass Spectrum: M+H⁺ 467.

Example 17**4-(3-bromo-6-chlorobenzofuran-7-ylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline**

Using an analogous procedure to that described in Example 3, 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (0.13 g) was reacted with 7-amino-3-bromo-6-chlorobenzofuran (0.186 g) to give the title compound (0.14 g); NMR Spectrum: (DMSO_d₆

- 75 -

and CF₃CO₂D) 2.3 (m, 2H), 3.15 (m, 2H), 3.35 (t, 2H), 3.55 (m, 2H), 3.7 (t, 2H), 4.0 (s, 3H), 4.05 (m, 2H), 4.35 (t, 2H), 7.4 (s, 1H), 7.7 (d, 2H), 8.2 (s, 1H), 8.4 (s, 1H), 8.85 (s, 1H); Mass Spectrum: M+H⁺ 549.

5 Example 18

Pharmaceutical compositions

The following illustrate representative pharmaceutical dosage forms of the invention as defined herein (the active ingredient being termed "Compound X"), for therapeutic or prophylactic use in humans:

10

(a)	Tablet I	mg/tablet
	Compound X.....	100
	Lactose Ph.Eur.....	182.75
	Croscarmellose sodium.....	12.0
15	Maize starch paste (5% w/v paste).....	2.25
	Magnesium stearate.....	3.0

20

(b)	Tablet II	mg/tablet
	Compound X.....	50
	Lactose Ph.Eur.....	223.75
	Croscarmellose sodium.....	6.0
	Maize starch.....	15.0
	Polyvinylpyrrolidone (5% w/v paste).....	2.25
	Magnesium stearate.....	3.0

25

(c)	Tablet III	mg/tablet
	Compound X.....	1.0
	Lactose Ph.Eur.....	93.25
	Croscarmellose sodium.....	4.0
30	Maize starch paste (5% w/v paste).....	0.75
	Magnesium stearate.....	1.0

- 76 -

	(d)	Capsule	mg/capsule
		Compound X.....	10
		Lactose Ph.Eur.....	488.5
		Magnesium.....	1.5
5			
	(e)	Injection I	(50 mg/ml)
		Compound X.....	5.0% w/v
		1M Sodium hydroxide solution.....	15.0% v/v
		0.1M Hydrochloric acid (to adjust pH to 7.6)	
10		Polyethylene glycol 400.....	4.5% w/v
		Water for injection to 100%	
	(f)	Injection II	(10 mg/ml)
		Compound X.....	1.0% w/v
15		Sodium phosphate BP.....	3.6% w/v
		0.1M Sodium hydroxide solution.....	15.0% v/v
		Water for injection to 100%	
	(g)	Injection III	(1mg/ml, buffered to pH6)
20		Compound X.....	0.1% w/v
		Sodium phosphate BP.....	2.26% w/v
		Citric acid.....	0.38% w/v
		Polyethylene glycol 400.....	3.5% w/v
		Water for injection to 100%	
25			
	(h)	Aerosol I	mg/ml
		Compound X.....	10.0
		Sorbitan trioleate.....	13.5
		Trichlorofluoromethane.....	910.0
30		Dichlorodifluoromethane.....	490.0

- 77 -

5	(i)	Aerosol II	mg/ml
		Compound X.....	0.2
		Sorbitan trioleate.....	0.27
		Trichlorofluoromethane.....	70.0
		Dichlorodifluoromethane.....	280.0
		Dichlorotetrafluoroethane.....	1094.0
10	(j)	Aerosol III	mg/ml
		Compound X.....	2.5
		Sorbitan trioleate.....	3.38
		Trichlorofluoromethane.....	67.5
		Dichlorodifluoromethane.....	1086.0
		Dichlorotetrafluoroethane.....	191.6
15	(k)	Aerosol IV	mg/ml
		Compound X.....	2.5
		Soya lecithin.....	2.7
		Trichlorofluoromethane.....	67.5
		Dichlorodifluoromethane.....	1086.0
20		Dichlorotetrafluoroethane.....	191.6
25	(l)	Ointment	ml
		Compound X.....	40 mg
		Ethanol.....	300 µl
		Water.....	300 µl
		1-Dodecylazacycloheptan-2-one.....	50 µl
		Propylene glycol.....	to 1 ml

Note

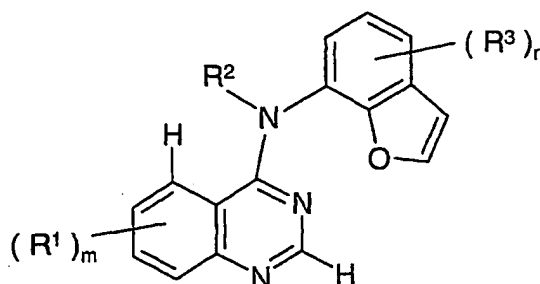
30 The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate. The aerosol formulations (h)-(k)

- 78 -

may be used in conjunction with standard, metered dose aerosol dispensers, and the suspending agents sorbitan trioleate and soya lecithin may be replaced by an alternative suspending agent such as sorbitan monooleate, sorbitan sesquioleate, polysorbate 80, polyglycerol oleate or oleic acid.

CLAIMS

1. A quinazoline derivative of the Formula I

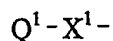


I

- 5 wherein m is 0, 1, 2 or 3;

each R^1 group, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, isocyano, nitro, hydroxy, mercapto, amino, formyl, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N -(1-6C)alkylcarbamoyl, N,N -di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N -(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N -(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino, N -(1-6C)alkyl-(3-6C)alkynoylamino, N -(1-6C)alkylsulphamoyl, N,N -di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and

15 N -(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



wherein X^1 is a direct bond or is selected from O, S, SO, SO₂, N(R⁴), CO, CH(OR⁴), CON(R⁴), N(R⁴)CO, SO₂N(R⁴), N(R⁴)SO₂, OC(R⁴)₂, SC(R⁴)₂ and N(R⁴)C(R⁴)₂, wherein R⁴ is hydrogen or (1-6C)alkyl, and Q¹ is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-

20 (1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl, or (R¹)_m is (1-3C)alkylenedioxy,

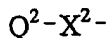
and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO₂, N(R⁵), CO, CH(OR⁵), CON(R⁵), N(R⁵)CO, SO₂N(R⁵), N(R⁵)SO₂, CH=CH and C≡C wherein

25 R⁵ is hydrogen or (1-6C)alkyl or, when the inserted group is N(R⁵), R⁵ may also be (2-6C)alkanoyl,

- 80 -

and wherein any $\text{CH}_2=\text{CH}-$ or $\text{HC}\equiv\text{C}-$ group within a R^1 substituent optionally bears at the terminal $\text{CH}_2=$ or $\text{HC}\equiv$ position a substituent selected from halogeno, carboxy, carbamoyl, (1-6C)alkoxycarbonyl, $\text{N}-(1-6\text{C})\text{alkylcarbamoyl}$, $\text{N,N-di-}[(1-6\text{C})\text{alkyl}]\text{carbamoyl}$, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or

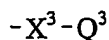
5 from a group of the formula :



wherein X^2 is a direct bond or is selected from CO and $\text{N}(\text{R}^6)\text{CO}$, wherein R^6 is hydrogen or (1-6C)alkyl, and Q^2 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

10 and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, $\text{N}-(1-6\text{C})\text{alkylcarbamoyl}$, $\text{N,N-di-}[(1-6\text{C})\text{alkyl}]\text{carbamoyl}$,

15 (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, $\text{N}-(1-6\text{C})\text{alkyl-}$ (2-6C)alkanoylamino, $\text{N}-(1-6\text{C})\text{alkylsulphamoyl}$, $\text{N,N-di-}[(1-6\text{C})\text{alkyl}]\text{sulphamoyl}$, (1-6C)alkanesulphonylamino and $\text{N}-(1-6\text{C})\text{alkyl-(1-6C)alkanesulphonylamino}$, or from a group of the formula :



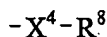
20 wherein X^3 is a direct bond or is selected from O, S, SO, SO_2 , $\text{N}(\text{R}^7)$, CO, $\text{CH}(\text{OR}^7)$, $\text{CON}(\text{R}^7)$, $\text{N}(\text{R}^7)\text{CO}$, $\text{SO}_2\text{N}(\text{R}^7)$, $\text{N}(\text{R}^7)\text{SO}_2$, $\text{C}(\text{R}^7)_2\text{O}$, $\text{C}(\text{R}^7)_2\text{S}$ and $\text{N}(\text{R}^7)\text{C}(\text{R}^7)_2$, wherein R^7 is hydrogen or (1-6C)alkyl, and Q^3 is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

25 and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino,

30 di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, $\text{N}-(1-6\text{C})\text{alkylcarbamoyl}$, $\text{N,N-di-}[(1-6\text{C})\text{alkyl}]\text{carbamoyl}$, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, $\text{N}-(1-6\text{C})\text{alkyl-(2-6C)alkanoylamino}$, $\text{N}-(1-6\text{C})\text{alkylsulphamoyl}$,

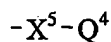
- 81 -

N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



wherein X^4 is a direct bond or is selected from O and N(R^9), wherein R^9 is hydrogen or

- 5 (1-6C)alkyl, and R^8 is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl, or from a group of the formula :



- 10 wherein X^5 is a direct bond or is selected from O, N(R^{10}) and CO, wherein R^{10} is hydrogen or (1-6C)alkyl, and Q^4 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl and (1-6C)alkoxy,

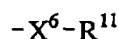
- 15 and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo or thioxo substituents;

R^2 is hydrogen or (1-6C)alkyl;

n is 0, 1, 2 or 3; and

R^3 is halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl,

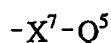
- 20 (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino, N-(1-6C)alkyl-(3-6C)alkynoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



wherein X^6 is a direct bond or is selected from O and N(R^{12}), wherein R^{12} is hydrogen or

- 30 (1-6C)alkyl, and R^{11} is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl or di-[(1-6C)alkyl]amino-(1-6C)alkyl, or from a group of the formula :

- 82 -



wherein X^7 is a direct bond or is selected from O, S, SO, SO₂, N(R¹³), CO, CH(OR¹³), CON(R¹³), N(R¹³)CO, SO₂N(R¹³), N(R¹³)SO₂, C(R¹³)₂O, C(R¹³)₂S and N(R¹³)C(R¹³)₂,

wherein R¹³ is hydrogen or (1-6C)alkyl, and Q⁵ is aryl, aryl-(1-6C)alkyl, heteroaryl,

- 5 heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl and (1-6C)alkoxy, and any heterocyclyl group within Q⁵ optionally bears 1 or 2 oxo or thioxo substituents, or a pharmaceutically-acceptable salt thereof.

10

2. A quinazoline derivative of the Formula I according to claim 1 wherein :

- m is 1 or 2 and each R¹ group, which may be the same or different, is located at the 6- and/or 7-positions and is selected from hydroxy, amino, methyl, ethyl, propyl, butyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, methylamino, ethylamino, dimethylamino, diethylamino, acetamido, propionamido, 2-imidazol-1-ylethoxy, 2-(1,2,4-triazol-1-yl)ethoxy, 15 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin- 20 4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy, 2-piperidin-3-ylethoxy, 3-piperidin-3-ylpropoxy, 2-piperidin-4-ylethoxy, 3-piperidin-4-ylpropoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 4-piperazin-1-ylbutoxy, 25 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O, NH, CH=CH and C≡C,

- and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each 30 said CH₂ or CH₃ group a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diethylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino, N-methyl-N-propylamino and acetoxo;

- 83 -

and wherein any heteroaryl or heterocyclyl group within a substituent on R¹ optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, methoxy, N-methylcarbamoyl and N,N-dimethylcarbamoyl and a pyrrolidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or

5 homopiperazin-1-yl group within a R¹ substituent is optionally N-substituted with 2-methoxyethyl, 3-methoxypropyl, cyanomethyl, 2-aminoethyl, 3-aminopropyl, 2-methylaminoethyl, 3-methylaminopropyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-piperazin-1-ylethyl or

10 3-piperazin-1-ylpropyl, the last 8 of which substituents each optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy,

and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1 or 2 oxo substituents;

15 R² is hydrogen;

n is 0 or 1 and the R³ group, if present, is located at the 5- or 6-position of the benzofuran ring and is selected from fluoro, chloro, trifluoromethyl, cyano, hydroxy, methyl, ethyl, vinyl, allyl, ethynyl, methoxy and ethoxy;

or a pharmaceutically-acceptable acid-addition salt thereof.

20

3. A quinazoline derivative of the Formula I according to claim 1 wherein :

m is 2 and the first R¹ group is located at the 6-position and is selected from hydroxy, methoxy, ethoxy and propoxy, and the second R¹ group is located at the 7-position and is selected from 2-dimethylaminoethoxy, 3-dimethylaminopropoxy, 4-dimethylaminobutoxy,

25 2-diethylaminoethoxy, 3-diethylaminopropoxy, 4-diethylaminobutoxy,

2-diisopropylaminoethoxy, 3-diisopropylaminopropoxy, 4-diisopropylaminobutoxy,

2-(N-isopropyl-N-methylamino)ethoxy, 3-(N-isopropyl-N-methylamino)propoxy,

4-(N-isopropyl-N-methylamino)butoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy,

4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, N-methylpyrrolidin-3-yloxy,

30 pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy,

2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy,

2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-

- 84 -

- 4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy,
 piperidin-3-yloxy, N-methylpiperidin-3-yloxy, piperidin-4-yloxy, N-methylpiperidin-4-yloxy,
 piperidin-3-ylmethoxy, N-methylpiperidin-3-ylmethoxy, piperidin-4-ylmethoxy,
N-methylpiperidin-4-ylmethoxy, 2-piperidin-3-ylethoxy, 2-(N-methylpiperidin-3-yl)ethoxy,
 5 3-piperidin-3-ylpropoxy, 3-(N-methylpiperidin-3-yl)propoxy, 2-piperidin-4-ylethoxy,
 2-(N-methylpiperidin-4-yl)ethoxy, 3-piperidin-4-ylpropoxy,
 3-(N-methylpiperidin-4-yl)propoxy, 2-(4-methylpiperazin-1-yl)ethoxy,
 3-(4-methylpiperazin-1-yl)propoxy, 4-(4-methylpiperazin-1-yl)butoxy,
 2-(4-cyanomethylpiperazin-1-yl)ethoxy, 3-(4-cyanomethylpiperazin-1-yl)propoxy,
 10 4-(4-cyanomethylpiperazin-1-yl)butoxy, 2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy,
 2-methylsulphonylethoxy and 3-methylsulphonylpropoxy,

and wherein any CH₂ group within the second R¹ group that is attached to two carbon atoms optionally bears a hydroxy group or acetoxy group on said CH₂ group,

- and wherein any heterocyclyl group within the second R¹ group optionally bears 1 or 2
 15 oxo substituents;

R² is hydrogen; and

n is 0 or n is 1 and the R³ group is located at the 5- or 6-position of the benzofuran ring and is selected from fluoro, chloro, trifluoromethyl, cyano, methyl, ethyl, ethynyl, methoxy and ethoxy;

- 20 or a pharmaceutically-acceptable acid-addition salt thereof.

4. A quinazoline derivative of the Formula I according to claim 1 wherein :

- m is 2 and the first R¹ group is located at the 6-position and is selected from hydroxy, methoxy, ethoxy and propoxy, and the second R¹ group is located at the 7-position and is
 25 selected from 2-dimethylaminoethoxy, 3-dimethylaminopropoxy, 2-diethylaminoethoxy, 3-diethylaminopropoxy, 2-diisopropylaminoethoxy, 3-diisopropylaminopropoxy,
 2-(N-isopropyl-N-methylamino)ethoxy, 3-(N-isopropyl-N-methylamino)propoxy,
 2-(N-isobutyl-N-methylamino)ethoxy, 3-(N-isobutyl-N-methylamino)propoxy,
 2-(N-allyl-N-methylamino)ethoxy, 3-(N-allyl-N-methylamino)propoxy,
 30 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-pyrrolidin-2-ylethoxy,
 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy,
 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-

- 85 -

- 4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, piperidin-3-ylmethoxy, N-methylpiperidin-3-ylmethoxy, piperidin-4-ylmethoxy, N-methylpiperidin-4-ylmethoxy, 2-piperidin-3-ylethoxy, 2-(N-methylpiperidin-3-yl)ethoxy, 3-piperidin-3-ylpropoxy, 3-(N-methylpiperidin-3-yl)propoxy, 2-piperidin-4-ylethoxy,
- 5 2-(N-methylpiperidin-4-yl)ethoxy, 3-piperidin-4-ylpropoxy, 3-(N-methylpiperidin-4-yl)propoxy, 3-homopiperidinopropoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 2-(4-cyanomethylpiperazin-1-yl)ethoxy and 3-(4-cyanomethylpiperazin-1-yl)propoxy,
- and wherein any CH₂ group within the second R¹ group that is attached to two carbon
- 10 atoms optionally bears a hydroxy group or acetoxy group on said CH₂ group,
- R² is hydrogen; and
- n is 0 or n is 1 or 2 and an R³ group, if present, is located at the 5- or 6-position of the benzofuran ring and is selected from fluoro, chloro, bromo, trifluoromethyl, cyano, methyl, ethyl, ethynyl, methoxy and ethoxy;
- 15 or a pharmaceutically-acceptable acid-addition salt thereof.

5. A quinazoline derivative of the Formula I according to claim 1 wherein :
- m is 2 and the first R¹ group is a 6-methoxy group and the second R¹ group is located at the 7-position and is selected from 3-(N-isopropyl-N-methylamino)propoxy,
- 20 3-(N-isobutyl-N-methylamino)propoxy, 3-pyrrolidin-1-ylpropoxy, 3-morpholinopropoxy, 3-piperidinopropoxy, piperidin-4-ylmethoxy, N-methylpiperidin-4-ylmethoxy, 3-homopiperidinopropoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy and 3-(4-cyanomethylpiperazin-1-yl)propoxy,
- and wherein any CH₂ group within the second R¹ group that is attached to two carbon
- 25 atoms optionally bears a hydroxy or acetoxy group on said CH₂ group;
- R² is hydrogen; and
- n is 0 or n is 1 and the R³ group is located at the 5- or 6-position of the benzofuran ring and is selected from fluoro and chloro;
- or a pharmaceutically-acceptable acid-addition salt thereof.

30

6. A quinazoline derivative of the Formula I according to claim 1 selected from :
- 4-(7-benzofuranylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,

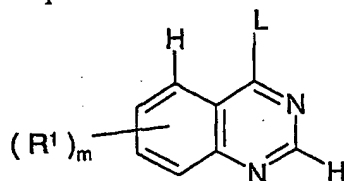
- 4-(7-benzofuranylamino)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,
4-(7-benzofuranylamino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,
4-(7-benzofuranylamino)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,
4-(3-chlorobenzofuran-7-ylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
5 4-(3-chlorobenzofuran-7-ylamino)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,
4-(3-chlorobenzofuran-7-ylamino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,
4-(3-chlorobenzofuran-7-ylamino)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,
4-(6-chlorobenzofuran-7-ylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
10 4-(6-chlorobenzofuran-7-ylamino)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,
4-(6-chlorobenzofuran-7-ylamino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,
4-(6-chlorobenzofuran-7-ylamino)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,
4-(5-fluorobenzofuran-7-ylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
15 4-(5-fluorobenzofuran-7-ylamino)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,
4-(5-fluorobenzofuran-7-ylamino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,
4-(5-fluorobenzofuran-7-ylamino)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,
4-(7-benzofuranylamino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline,
20 7-(2-acetoxy-3-pyrrolidin-1-ylpropoxy)-4-(3-chlorobenzofuran-7-ylamino)-6-methoxyquinazoline,
7-[2-acetoxy-3-(N-isopropyl-N-methylamino)propoxy]-4-(3-chlorobenzofuran-7-ylamino)-6-methoxyquinazoline,
7-[2-acetoxy-3-(4-cyanomethylpiperazin-1-yl)propoxy]-4-(3-chlorobenzofuran-7-ylamino)-
25 6-methoxyquinazoline,
7-(2-acetoxy-3-piperidinopropoxy)-4-(3-chlorobenzofuran-7-ylamino)-6-methoxyquinazoline,
4-(3-chlorobenzofuran-7-ylamino)-7-(2-hydroxy-3-pyrrolidin-1-ylpropoxy)-6-methoxyquinazoline,
4-(3-chlorobenzofuran-7-ylamino)-7-[2-hydroxy-3-(N-isopropyl-N-methylamino)propoxy]-
30 6-methoxyquinazoline,
4-(3-chlorobenzofuran-7-ylamino)-7-[3-(4-cyanomethylpiperazin-1-yl)-2-hydroxypropoxy]-6-methoxyquinazoline and

- 87 -

4-(3-chlorobenzofuran-7-ylamino)-7-(2-hydroxy-3-piperidinopropoxy)-
6-methoxyquinazoline;
or a pharmaceutically-acceptable acid-addition salt thereof.

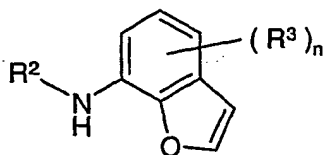
- 5 7. A process for the preparation of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, according to claim 1 which comprises :-

(a) the reaction of a quinazoline of the Formula II



II

wherein L is a displaceable group and m and R¹ have any of the meanings defined in claim 1
10 except that any functional group is protected if necessary, with an aniline of the Formula III



III

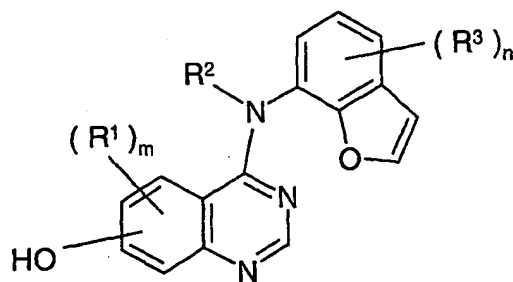
wherein R², n and R³ have any of the meanings defined in claim 1 except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means;

- 15 (b) for the production of those compounds of the Formula I wherein at least one R¹ group is a group of the formula



wherein Q¹ is an aryl-(1-6C)alkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl-(1-6C)alkyl or heterocyclyl-(1-6C)alkyl group or an optionally
20 substituted alkyl group and X¹ is an oxygen atom, the coupling of a quinazoline of the Formula V

- 88 -



V

wherein m , R^1 , R^2 , n and R^3 have any of the meanings defined in claim 1 except that any functional group is protected if necessary, with an appropriate alcohol wherein any functional group is protected if necessary whereafter any protecting group that is present is removed by

5 conventional means;

(c) for the production of those compounds of the Formula I wherein an R^1 group contains a primary or secondary amino group, the cleavage of the corresponding compound of the Formula I wherein the R^1 group contains a protected primary or secondary amino group;

(d) for the production of those compounds of the Formula I wherein an R^1 group contains

10 a (1-6C)alkoxy or substituted (1-6C)alkoxy group or a (1-6C)alkylamino or substituted (1-6C)alkylamino group, the alkylation of a quinazoline derivative of the formula I wherein the R^1 group contains a hydroxy group or a primary or secondary amino group as appropriate;

(e) for the production of those compounds of the Formula I wherein R^1 is an amino-hydroxy-disubstituted (1-6C)alkoxy group, the reaction of a compound of the Formula

15 I wherein the R^1 group contains an epoxy-substituted (1-6C)alkoxy group with a heterocyclyl compound or an appropriate amine; or

(f) for the production of those compounds of the Formula I wherein an R^1 group contains a hydroxy group, the cleavage of the corresponding compound of the Formula I wherein the R^1 group contains a protected hydroxy group;

20 and when a pharmaceutically-acceptable salt of a quinazoline derivative of the Formula I is required it may be obtained using a conventional procedure.

8. A pharmaceutical composition which comprises a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined in claim 1 in association

25 with a pharmaceutically-acceptable diluent or carrier.

- 89 -

9. A quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined in claim 1 for use in a method of treatment of the human or animal body by therapy.
- 5 10. The use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined in claim 1 in the manufacture of a medicament for use as an anti-invasive agent in the containment and/or treatment of solid tumour disease.

INTERNATIONAL SEARCH REPORT

PCT/GB 01/04498

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D405/12 A61K31/517 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 866 572 A (JOHNSTONE CRAIG ET AL) 2 February 1999 (1999-02-02) column 1, line 3 - line 12 column 4, line 57 - line 61; claim 1	1-10
A	US 5 821 246 A (THOMAS ANDREW PETER ET AL) 13 October 1998 (1998-10-13) column 1, line 3 - line 12; claim 1	1-10
A	WO 98 13354 A (LOHMANN JEAN JACQUES MARCEL ;HENNEQUIN LAURENT FRANCOIS AND (FR);) 2 April 1998 (1998-04-02) page 2, line 23 - page 3, line 13; claim 1	1-10



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

7 January 2002

Date of mailing of the international search report

16/01/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Seelmann, I

INTERNATIONAL SEARCH REPORT

PCT/GB 01/04498

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5866572	A	02-02-1999	AU 707339 B2	08-07-1999
			AU 1612697 A	02-09-1997
			CA 2242102 A1	21-08-1997
			CN 1211240 A	17-03-1999
			EP 0880507 A1	02-12-1998
			WO 9730034 A1	21-08-1997
			JP 2000504713 T	18-04-2000
			NO 983707 A	13-10-1998
US 5821246	A	13-10-1998	AT 175962 T	15-02-1999
			AU 703328 B2	25-03-1999
			AU 3813095 A	06-06-1996
			CA 2200871 A1	23-05-1996
			DE 69507505 D1	04-03-1999
			DE 69507505 T2	02-06-1999
			DK 790986 T3	13-09-1999
			EP 0790986 A1	27-08-1997
			ES 2128092 T3	01-05-1999
			FI 971970 A	07-05-1997
			WO 9615118 A1	23-05-1996
			JP 10508616 T	25-08-1998
			NO 972152 A	12-05-1997
			NZ 294917 A	25-02-1999
			ZA 9509572 A	13-05-1996
WO 9813354	A	02-04-1998	AU 729968 B2	15-02-2001
			AU 4561397 A	17-04-1998
			BR 9711302 A	17-08-1999
			CN 1231662 A	13-10-1999
			CZ 9901039 A3	16-06-1999
			EP 0929530 A1	21-07-1999
			WO 9813354 A1	02-04-1998
			JP 2001500891 T	23-01-2001
			NO 991422 A	24-03-1999
			PL 332385 A1	13-09-1999
			SK 38999 A3	08-10-1999
			TR 9900674 T2	21-07-1999
			HU 9902850 A2	28-04-2000